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(54) Title: MODULATION OF MUC1 MEDIATED SIGNAL TRANSDUCTION

(57) Abstract: The present invention provides compositions and methods for inhibiting the binding of the carboxy-terminus of MUC1 to PDZ domain(s) and to enhance the sensitivity of MUC1 expressing cancer cells to chemotherapeutic agents.



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DESCRIPTION

MODULATION OF MUC1 MEDIATED SIGNAL TRANSDUCTION

5 This application claims priority to U.S. Provisional Application Serial No: 60/462,111, filed April 11, 2003, U.S. Provisional Application Serial No: 60/467,728, filed May, 2, 2003, U.S. Provisional Application Serial No: 60/475,595, filed June 4, 2003, U.S. Provisional Application Serial No: 60/502,111, filed September 11, 2003 and U.S. Provisional Application Serial No: 60/524,188, filed November 21, 2003, all herein
10 incorporated by reference

BACKGROUND OF THE INVENTION

The present invention relates generally to the field of cancer therapy and more specifically to the use of modulators or agents that interact with MUC1 as a point on intervention in cancer therapy.

15 The human MUC1 mucin glycoprotein is expressed on the apical borders of secretory epithelial cells on the luminal surface of most glandular epithelia (Kufe et al., 1984). In carcinomas, MUC1 is highly overexpressed throughout the entire cell membrane and cytoplasm (Kufe et al., 1984; Perey et al., 1992). As such, the aberrant pattern of MUC1 expression in carcinoma cells may confer a function for MUC1 normally found at the apical
20 membrane to the entire cell membrane. The hallmark of MUC1 mucin is an ectodomain comprising a glycosylated 20 amino acid extracellular sequence that is tandemly repeated 25-100 times in each molecule (Strouss & Decker, 1992). The mucin glycosylation level appears to be lower in cancer cells than normal cells of ductal epithelial tissue (Kufe, U.S. Pat. No. 5,506,343). This hypoglycosylation results in the exposure of tumor-specific epitopes that are
25 hidden in the fully glycosylated mucin.

Over ninety percent of breast cancers show an increased expression of MUC1 (also known as Mucin, Epithelial Membrane Antigen, Polymorphic Epithelial Mucin, Human Milk Fat Globule Membrane antigen, Episialin, DF-3, etc., see Barry & Sharkey, 1985). Several clinical studies have suggested that mucinous tumor antigens expressed on the cell surface of
30 tumor cells associate with poor prognosis of a variety of cancer types (Itzkowitz et al., 1990).

MUC1 is expressed as both a transmembrane form and a secreted form (Finn et al., 1995). The repeating sialyl epitopes of MUC1 (the "ectodomain") are shed into the serum (Reddish et al., 1996). The N-terminal ectodomain (the extracellular domain that is cleaved) of MUC1 consists of a variable number of the 20-amino acid tandem repeats that are subject

to O-glycosylation. This mucin extends far above the cell surface and past the glycocalyx making it easily available for interactions with other cells. The C-terminal region of MUC1 includes a 37 amino acid transmembrane domain and a 72 amino acid cytoplasmic tail that contains sites for tyrosine phosphorylation. An approximately 45-amino acid extracellular domain remains following cleavage of the ectodomain. It is not known what enzyme is responsible for the cleavage of the ectodomain at this time.

The cytoplasmic domain of MUC1 ("MUC1/CD") encompasses multiple sub-domains that are important in intracellular signaling in cancer cells. β -catenin binds directly to MUC1/CD at a SAGNGGSSL motif (Yamamoto et al., 1997). β -catenin, a component of the adherens junctions of mammalian epithelium, binds to cadherins at the intracellular surface of the plasma membrane and performs a signaling role in the cytoplasm as the penultimate downstream mediator of the wnt signaling pathway (Takeichi, 1990; Novak & Dedhar, 1999). The ultimate mediator of the wnt pathway is a nuclear complex of β -catenin and lymphoid enhancer factor/T cell factor (Lef/Tcf) that stimulates the transcription of a variety of target genes (see e.g., Molenaar et al., 1996; Brunner et al., 1997). Defects in the β -catenin-Lef/Tcf pathway are involved in the development of several types of cancers (Novak & Dedhar, 1999).

Glycogen synthase kinase 3β (GSK3 β) also binds directly to MUC1/CD and phosphorylates serine in a DRSPY site adjacent to the β -catenin binding motif, thereby decreasing the association between MUC1 and β -catenin (Li et al., 1998). In addition, the c-Src tyrosine kinase also binds to and phosphorylates a MUC1/CD SPYEKV motif, resulting in an increased interaction between MUC1/CD and β -catenin and a decreased interaction between MUC1/CD and GSK3 β (Li et al., 2001).

MUC1 associates also constitutively with the epidermal growth factor receptor (EGF-R, HER1) at the cell membrane and activated EGF-R induces phosphorylation of the MUC1/CD SPYEKV motif (Li et al., 2001(a)). EGF-R mediated phosphorylation of MUC1/CD appears to increase the interaction of MUC1 with c-Src and β -catenin and downregulate the interaction between MUC1 and GSK3 β . These results support a model wherein MUC1 integrates the signaling among c-Src, β -catenin and GSK3 β pathways and dysregulation of this integrated signaling by aberrant overexpression of MUC1 in cancer cells could promote the transformed phenotype (Li et al., 2001(a)).

The Armadillo protein p120^{cas} also binds directly to MUC1/CD resulting in the nuclear localization of p120 (Li & Kufe, 2001). p120 has been implicated in cell

transformation and altered patterns of p120 expression have been observed in carcinomas (see e.g., Jawhari et al., 1999; Shimazui et al., 1996). p120 is a v-Src tyrosine kinase substrate, binds to E-cadherin, and is implicated as a transcriptional coactivator (Reynolds et al., 1989; Reynolds et al., 1994; Daniels & Reynolds, 1999). The observation that p120 localizes to both cell junctions and the nucleus, have supported a role for p120, like β -catenin, in the regulation of both cell adhesion and gene transcription. Decreased cell adhesion resulting from association of MUC1 and p120 may be involved in increased metastatic potential of MUC1-expressing tumor cells.

Thus, the available evidence indicates that MUC1/CD functions to transfer signals from the extracellular domain to the nucleus, and utilizes signaling mechanisms that have been implicated in adhesion receptor and growth factor signaling and cellular transformation. It is desirable to identify compositions and methods related to modulation of the MUC1-mediated signaling and its putative role in cellular transformation.

SUMMARY OF THE INVENTION

The present invention provides methods for inhibiting the binding of the cytoplasmic domain of MUC1 to a PDZ domain, wherein the PDZ domain may suitably be ZO-1 d2, SIP1 d1, LIM MYSTIQUE, AIPC, KIAA0751, MAST2, PRIL-16 d1, GRIP2 d5, SITAC 18, NSP or KIAA1526 d1, and wherein the PDZ domain may be within a MUC1-expressing cancer, enhancing the sensitivity of MUC1-expressing cancer cells to chemotherapeutic agents comprising contacting the MUC1-expressing cancer cell with an effective amount of an agent that inhibits the binding of MUC1 to a PDZ domain; killing MUC1-expressing cancer cells comprising contacting the MUC1-expressing cancer cells with an effective amount of a chemotherapeutic agent and an agent that inhibits the binding of MUC1 to a PDZ domain; inhibiting the proliferation of MUC1-expressing cancer cells comprising contacting the MUC1-expressing cancer cells with an effective amount of an agent that inhibits the binding of MUC1 to a PDZ domain; treating a MUC1-expressing cancer by administering an effective amount of an agent that inhibits the binding of MUC1 to a PDZ domain; treating a MUC1-expressing cancer by administering an effective amount of an agent that inhibits the binding of MUC1 to a PDZ domain and an effective amount of a chemotherapeutic agent; and inhibiting the colocalization or association of MUC1 with one or more of the proteins FGFR, EGFR, ErbB2, ErbB3, ErbB4, β -catenin, γ -catenin, c-SRC or GSK3 β .

Agents that inhibit the binding of MUC1 to a PDZ domain suitably include peptides of the formula X^1 -aa²-aa¹-aa⁰, wherein aa⁰ is a hydrophobic aliphatic amino acid residue or a

hydrophobic aromatic amino acid residue, aa² is a hydrophobic aliphatic amino acid residue, hydrophobic aromatic amino acid residue, polar amino acid residue, basic amino acid residue or an acidic amino acid residue, aa¹ is an amino acid residue and X¹ is a sequence of 0 to 50 amino acid residues. In some embodiments, aa⁰ is V, L, A, I, S or Y and aa² is V, L, A, I, F, Y, W, Q, N, S, T, R, K, D or B. In some embodiments, aa²-aa¹-aa⁰ is a sequence selected from SEQ ID NO: 1 through SEQ ID NO: 40. In some embodiments, the carboxy-terminus of the peptide of formula X¹-aa²-aa¹-aa⁰ comprises the carboxy-terminal 4, 5, 6, 7, 8 or 9 amino acid residues of a nine amino acid residue sequence selected from SEQ ID NO: 41 through SEQ ID NO: 94. In some embodiments, the carboxy-terminus of the peptide of formula X¹-aa²-aa¹-aa⁰ comprises the carboxy-terminal 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 amino acid residues of SEQ ID NO: 95 or SEQ ID NO: 96. In some embodiments, the amino-terminus of X¹ of the peptide X¹-aa²-aa¹-aa⁰ comprises X²-X³, wherein X² is a transmembrane transporter peptide sequence and X³ is an optional linker sequence. In some embodiments, X² is a sequence selected from SEQ ID NO: 97 through SEQ ID NO: 127. In some embodiments, X² is SEQ ID NO: 102, SEQ ID NO: 108 or SEQ ID NO: 119.

In embodiments that encompass a cancer cell, the cancer cell may be a breast cancer cell, an ovarian cancer cell, a lung cancer cell, a pancreatic cancer cell, a prostate cancer cell, a stomach cancer cell, a small intestine cancer cell, a colon cancer cell, a liver cancer cell, a kidney cancer cell, an esophageal cancer cell, a head and neck cancer cell, a testicular cancer cell, a blood cancer cell, a bone marrow cancer cell, or a cancer cell of another tissue. In some embodiments, the cancer cell is within a patient.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

FIG. 1: 293 cells were transfected to express pIRESpuro2-Flag-MUC1-CD(1-72) or pIRESpuro2-Flag-MUC1-CD(1-68). Lysates were subjected to immunoprecipitation with anti-FGFR3 or IgG as a control. The immunoprecipitates and lysate not subjected to immunoprecipitation were analyzed by immunoblotting with anti-MUC1-CD.

FIG. 2: 293 cells were transfected to express pIRESpuro2-Flag-MUC1-CD(1-72) or pIRESpuro2-Flag-MUC1-CD(1-68). Lysates were subjected to immunoprecipitation with

anti-EGFR or IgG as a control. The immunoprecipitates and lysate not subjected to immunoprecipitation were analyzed by immunoblotting with anti-MUC1-CD.

FIG. 3: Profile of the binding of 0.01 μ M C-terminus of MUC1 to PDZ domains.

FIG. 4: Profile of the binding of 0.1 μ M C-terminus of MUC1 to PDZ domains.

- 5 **FIG. 5:** Summary of effects of the knockdown of Lim Mystique (LIM-M) or KIAA0751, aka RIM2 (KIAA) on CDDP-induced apoptosis in A549 and HCT116/MUC1 cells. At 48 hr after transfection of siRNAs specific for Lim Mystique or KIAA0751, cells were treated with or without 100 μ M CDDP for 24 hr and then analyzed for apoptosis.

- 10 **FIG. 6:** Summary of effects of the knockdown of KIAA0751, aka RIM2 (KIAA) on CDDP-induced apoptosis in HCT116/Vector cells. At 48 hr after transfection of siRNA specific for KIAA0751, cells were treated with 0, 10 and 100 μ M CDDP for 24 hr and then analyzed for apoptosis.

- 15 **FIG. 7:** Summary of effects of the knockdown of KIAA0751, aka RIM2 (KIAA) or ZO-1 on CDDP-induced apoptosis in HCT116/MUC1 cells. At 48 hr after transfection of siRNA specific for KIAA0751 or ZO-1 SIP1, cells were treated with or without 100 μ M CDDP for 24 hr and 48 hr and then analyzed for apoptosis.

- 20 **FIG. 8:** Summary of effects of the knockdown of SIP1 on CDDP-induced apoptosis in A549 or HCT116/MUC1 cells. At 48 hr after transfection of siRNA specific for SIP1, cells were treated with or without 100 μ M CDDP for 24 hr and 48 hr and then analyzed for apoptosis.

FIG. 9: Summary of results of titration of RIM2 (KIAA0751) and ZO1 d2 with two biotinylated carboxy-terminal MUC1 isotypes, i.e., with an A/T substitution at the fifth amino acid residue from the carboxy-terminus (AAA and AAT). Results indicate similar binding affinities for both ZO1 d2 and RIM2.

- 25 **FIG. 10:** Summary of results of competitive inhibition of selected peptides of the binding of biotinylated TAT-MUC1 to RIM2

FIG. 11: Summary of results of screening the binding of 0.01 μ M biotinylated SEQ ID NO: 137 to PDZ domains.

- 30 **FIG. 12:** Summary of results of screening the binding of 0.025 μ M biotinylated SEQ ID NO: 136 to PDZ domains.

FIG. 13: Summary of results of screening the binding of 0.05 μ M biotinylated SEQ ID NO: 138 to PDZ domains.

DETAILED DESCRIPTION OF THE INVENTION

I. PDZ Domains and Related Ligands

PDZ domains are modular protein interaction domains that play a cellular role in protein targeting and protein complex assembly. These domains are relatively small (≥ 90 residues), fold into a compact globular structure and generally have N- and C-termini that are close to one another in the folded structure. Thus the domains are highly modular and could easily have been integrated into existing proteins without significant structural disruption through the course of evolution. PDZ domains typically consists of six β -strands (βA - βF) and two α -helices (αA and αB). Peptide ligands bind in an extended groove between strand βB and helix αB by a mechanism referred to as β -strand addition, wherein the peptide serves as an extra β -strand that is added onto the edge of a pre-existing β -sheet within the PDZ domain (Harrison, 1996).

PDZ domains recognize specific C-terminal sequence motifs that are usually about four to five residues in length (Niethammer et al., 1998). One nomenclature utilized for residues within the PDZ-binding motif refers to the C-terminal residue as the P_0 residue and subsequent residues towards the N-terminus are termed P_{-1} , P_{-2} , P_{-3} , etc. Extensive peptide library screens suggest that the P_0 and P_{-2} residues are most critical for recognition (Songyang et al., 1997; Schultz et al., 1998). These studies also show that PDZ domains can be divided into at least three main classes on the basis of their preferences for residues at these two sites: class I PDZ domains recognize the motif S/T-X- Φ -COOH (where Φ is a hydrophobic amino acid and X is any amino acid); class II PDZ domains recognize the motif Φ -X- Φ -COOH; and class III PDZ domains recognize the motif X-X-C-COOH. There are a few other PDZ domains that do not fall into any of these specific classes.

The four terminal amino acids of the cytoplasmic domain of MUC1 are serine, alanine, asparagine and leucine. Both leucine and alanine are hydrophobic amino acids, albeit that alanine is significantly less hydrophobic than leucine. This carboxy-terminal region of MUC1 is highly conserved over a number of species suggesting that this sequence is directed towards some cellular functionality. The present invention identifies the MUC1 carboxy-terminus as a ligand for select PDZ domains.

II. Peptides

A "fusion protein" or "fusion polypeptide" as used herein refers to a composite protein, i.e., a single contiguous amino acid sequence, made up of two (or more) distinct, heterologous polypeptides that are not normally fused together in a single amino acid

sequence. Thus, a fusion protein can include a single amino acid sequence that contains two entirely distinct amino acid sequences or two similar or identical polypeptide sequences, provided that these sequences are not normally found together in the same configuration in a single amino acid sequence found in nature. Fusion proteins can generally be prepared using either recombinant nucleic acid methods, i.e., as a result of transcription and translation of a recombinant gene fusion product, which fusion comprises a segment encoding a polypeptide of the invention and a segment encoding a heterologous protein, or by chemical synthesis methods well known in the art.

As used herein, the term "PDZ domain" refers to protein sequence (i.e., modular protein domain) of less than approximately 90 amino acids (i.e., about 80-90, about 70-80, about 60-70 or about 50-60 amino acids), characterized by homology to the brain synaptic protein PSD-95, the *Drosophila* septate junction protein Discs-Large (DLC), and the epithelial tight junction protein ZO1 (ZO1). PDZ domains are also known as Discs-Large homology repeats ("DHRs") and GLGF repeats. PDZ domains generally appear to maintain a core consensus sequence (Doyle, 1996).

Exemplary PDZ domain-containing proteins and PDZ domain sequences are shown in Table 3 in Example 6. The term "PDZ domain" also encompasses variants (e.g., naturally-occurring variants) of the sequences (e.g., polymorphic variants, variants with conservative substitutions, and the like) and domains from alternative species (e.g., mouse, rat). Typically, PDZ domains are substantially identical to those shown in U.S. Serial No. 09/724553, e.g., at least about 70%, at least about 80%, or at least about 90% amino acid residue identity when compared and aligned for maximum correspondence. The percentage of sequence identity, also termed homology, between a polypeptide native and a variant sequence may be determined by comparing the two sequences using the GAP program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, Madison Wisconsin), which uses the algorithm of Smith and Waterman (1981). It is appreciated in the art that PDZ domains can be mutated to give amino acid changes that can strengthen or weaken binding and to alter specificity, yet they remain PDZ domains (Schneider et al. 1998). Unless otherwise indicated, a reference to a particular PDZ domain (e.g., KIAA0751 or PRIL-16 d1) is intended to encompass the particular PDZ domain and variants that bind the same relevant protein ligand as the native protein, (e.g., MUC1-binding variants of KIAA0751 or PRIL-16 d1). In other words, if a reference is made to a particular PDZ domain, a reference is also made to variants of that PDZ domain wherein the variant is

competent to bind the relevant protein ligand, e.g., cytoplasmic tail of MUC1, as described herein.

As used herein, the term "PDZ protein" refers to a naturally-occurring protein containing a PDZ domain. Exemplary PDZ proteins include ZO-1, SIP1, LIM MYSITIQUE, AIPC, KIAA0751, MAST2, PRIL-16, GRIP2, SITAC 18, NSP, and KIAA1526.

As used herein, the term "PDZ-domain polypeptide" refers to a polypeptide containing a PDZ domain, such as a fusion protein including a PDZ domain sequence, a naturally-occurring PDZ protein, or an isolated PDZ domain peptide. A PDZ-domain polypeptide may therefore be about 60 amino acids or more in length, about 70 amino acids or more in length, about 80 amino acids or more in length, about 90 amino acids or more in length, about 100 amino acids or more in length, about 200 amino acids or more in length, about 300 amino acids or more in length, about 500 amino acids or more in length, about 800 amino acids or more in length, about 1000 amino acids or more in length, usually up to about 2000 amino acids or more in length. PDZ domain peptides are usually no more than about 100 amino acids (e.g., 50-60 amino acids, 60-70 amino acids, 80-90 amino acids, or 90-100 amino acids), and encode a PDZ domain.

As used herein, the term "PL protein" or "PDZ Ligand protein" refers to a naturally-occurring protein that forms a molecular complex with a PDZ-domain, or to a protein whose carboxy-terminus, when expressed separately from the full length protein (e.g., as a peptide fragment of 4-25 residues, e.g., 8, 10, 12, 14 or 16 residues), forms such a molecular complex. The molecular complex can be observed *in vitro* using the binding assays described herein. This definition is not intended to include anti-PDZ antibodies and the like.

As used herein, a "PL sequence" refers to the amino acid sequence of the C-terminus of a PL protein (e.g., the C-terminal 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 20 or 25 residues) ("C-terminal PL sequence") or to an internal sequence known to bind a PDZ domain ("internal PL sequence").

As used herein, a "PL peptide" is a peptide of having a sequence from, or based on, the sequence of the C-terminus of a PL protein. Exemplary MUC1 PL peptides (biotinylated) are listed in Table 8.

As used herein, a "PL fusion protein" is a fusion protein that has a PL sequence as one domain, typically as the C-terminal domain of the fusion protein. An exemplary PL fusion protein is a TAT-PL sequence fusion.

As used herein, the term "PL inhibitor peptide sequence" refers to PL peptide amino acid sequence that (in the form of a peptide or PL fusion protein) inhibits the interaction

between a PDZ domain polypeptide and a PL peptide (e.g., as measured by the binding assays described herein).

As used herein, a "PDZ-domain encoding sequence" means a segment of a polynucleotide encoding a PDZ domain. In various embodiments, the polynucleotide is DNA, RNA, single-stranded or double-stranded.

As used herein, the terms "antagonist" and "inhibitor," when used in the context of modulating a binding interaction (such as the binding of a PDZ domain sequence to a PL sequence), are used interchangeably and refer to an agent that reduces the binding of the, e.g., PL sequence (e.g., PL peptide) and the, e.g., PDZ domain sequence (e.g., PDZ protein, PDZ domain peptide).

As used herein, the terms "peptide mimetic," "peptidomimetic," and "peptide analog" are used interchangeably and refer to a synthetic chemical compound that has substantially the same structural and/or functional characteristics of a PL inhibitory or PL binding peptide of the invention. The mimetic can be either entirely composed of synthetic, non-natural analogues of amino acids, or, is a chimeric molecule of partly natural peptide amino acids and partly non-natural analogs of amino acids. The mimetic can also incorporate any amount of natural amino acid conservative substitutions as long as such substitutions also do not substantially alter the mimetic's structure and/or inhibitory or binding activity. As with polypeptides of the invention which are conservative variants, routine experimentation will determine whether a mimetic is within the scope of the invention, i.e., that its structure and/or function is not substantially altered. Thus, a mimetic composition is within the scope of the invention if it is capable of binding to a PDZ domain and/or inhibiting a PL-PDZ interaction.

Polypeptide mimetic compositions can contain any combination of nonnatural structural components, which are typically from three structural groups: a) residue linkage groups other than the natural amide bond ("peptide bond") linkages; b) non-natural residues in place of naturally occurring amino acid residues; or c) residues which induce secondary structural mimicry, i.e., to induce or stabilize a secondary structure, e.g., a beta turn, gamma turn, beta sheet, alpha helix conformation, and the like.

A polypeptide can be characterized as a mimetic when all or some of its residues are joined by chemical means other than natural peptide bonds. Individual peptidomimetic residues can be joined by peptide bonds, other chemical bonds or coupling means, such as, e.g., glutaraldehyde, N-hydroxysuccinimide esters, bifunctional maleimides, N,N-dicyclohexylcarbodiimide (DCC) or N,N'-diisopropylcarbodiimide (DIC). Linking groups that can be an alternative to the traditional amide bond ("peptide bond") linkages include,

e.g., ketomethylene (e.g., $-C(=O)-CH_2-$ for $-C(=O)-NH-$), aminomethylene (CH_2-NH), ethylene, olefin ($CH=CH$), ether (CH_2-O), thioether (CH_2-S), tetrazole (CN_4), thiazole, retroamide, thioamide, or ester (see, e.g., Spatola (1983) in *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*, Vol. 7, pp 267-357, A Peptide Backbone Modifications, Marcel Dekker, NY).

A polypeptide can also be characterized as a mimetic by containing all or some non-natural residues in place of naturally-occurring amino acid residues. Nonnatural residues are well described in the scientific and patent literature; a few exemplary nonnatural compositions useful as mimetics of natural amino acid residues and guidelines are described below.

Mimetics of aromatic amino acids can be generated by replacing by, e.g., D- or L-naphthylalanine; D- or L-phenylglycine; D- or L-2-thienylalanine; D- or L-1-, -2, -3-, or -4-pyrenylalanine; D- or L-3-thienylalanine; D- or L-(2-pyridinyl)-alanine; D- or L-(3-pyridinyl)-alanine; D- or L-(2-pyrazinyl)-alanine; D- or L-(4-isopropyl)-phenylglycine; D-(trifluoromethyl)-phenylglycine; D-(trifluoromethyl)-phenylalanine; D-p-fluorophenylalanine; D- or L-p-biphenylphenylalanine; K- or L-p-methoxybiphenylphenylalanine; D- or L-2-indole(alkyl)alanines; and, D- or L-alkylamines, where alkyl can be substituted or unsubstituted methyl, ethyl, propyl, hexyl, butyl, pentyl, isopropyl, iso-butyl, sec-isotyl, iso-pentyl, or a non-acidic amino acids. Aromatic rings of a nonnatural amino acid include, e.g., thiazolyl, thiophenyl, pyrazolyl, benzimidazolyl, naphthyl, furanyl, pyrrolyl, and pyridyl aromatic rings.

Mimetics of acidic amino acids can be generated by substitution by, e.g., non-carboxylate amino acids while maintaining a negative charge; (phosphono)alanine; sulfated threonine. Carboxyl side groups (e.g., aspartyl or glutamyl) can also be selectively modified by reaction with carbodiimides ($R=N-C-N-R$) such as, e.g., 1-cyclohexyl-3(2-morpholinyl)-(4-ethyl) carbodiimide or 1-ethyl-3(4-azonia- 4,4- dimethylpentyl) carbodiimide. Aspartyl or glutamyl can also be converted to asparaginyl and glutaminyl residues by reaction with ammonium ions.

Mimetics of basic amino acids can be generated by substitution with, e.g., (in addition to lysine and arginine) the amino acids ornithine, citrulline, or (guanidino)-acetic acid, or (guanidino)alkyl-acetic acid, where alkyl is defined above. Nitrile derivative (e.g., containing the CN -moiety in place of $COOH$) can be substituted for asparagine or glutamine. Asparaginyl and glutaminyl residues can be deaminated to the corresponding aspartyl or glutamyl residues.

Arginine residue mimetics can be generated by reacting arginyl with, e.g., one or more conventional reagents, including, e.g., phenylglyoxal, 2,3-butanedione, 1,2-cyclohexanedione, or ninhydrin, preferably under alkaline conditions.

- 5 Tyrosine residue mimetics can be generated by reacting tyrosyl with, e.g., aromatic diazonium compounds or tetranitromethane. N-acetylimidazol and tetranitromethane can be used to form O-acetyl tyrosyl species and 3-nitro derivatives, respectively.

- 10 Cysteine residue mimetics can be generated by reacting cysteinyl residues with, e.g., alpha-haloacetates such as 2-chloroacetic acid or chloroacetamide and corresponding amines, to give carboxymethyl or carboxyamidomethyl derivatives. Cysteine residue mimetics can also be generated by reacting cysteinyl residues with, e.g., bromo-trifluoroacetone, alpha-bromo-beta-(5-imidazolyl) propionic acid; chloroacetyl phosphate, N-alkylmaleimides, 3-nitro-2-pyridyl disulfide; methyl 2-pyridyl disulfide; p-chloromercuribenzoate; 2-chloromercuri-4 nitrophenol; or, chloro-7-nitrobenzo-oxa-1,3-diazole.

- 15 Lysine mimetics can be generated (and amino terminal residues can be altered) by reacting lysinyl with, e.g., succinic or other carboxylic acid anhydrides. Lysine and other alpha-amino-containing residue mimetics can also be generated by reaction with imidoesters, such as methyl picolinimidate, pyridoxal phosphate, pyridoxal, chloroborohydride, trinitrobenzenesulfonic acid, O-methylisourea, 2,4, pentanedione, and transamidase-catalyzed reactions with glyoxylate.

- 20 Mimetics of methionine can be generated by reaction with, e.g., methionine sulfoxide. Mimetics of proline include, e.g., pipecolic acid, thiazolidine carboxylic acid, 3- or 4-hydroxy proline, dehydropipecolic acid, 3- or 4-methylproline, or 3,3-dimethylproline. Histidine residue mimetics can be generated by reacting histidyl with, e.g., diethylprocarbonate or para-bromophenacyl bromide.

- 25 Other mimetics include, e.g., those generated by hydroxylation of proline and lysine; phosphorylation of the hydroxyl groups of seryl or thronyl residues; methylation of the alpha-amino groups of lysine, arginine and histidine; acetylation of the N-terminal amine; methylation of main chain amide residues or substitution with N-methyl amino acids; or amidation of C-terminal carboxyl groups.

- 30 A component of a natural polypeptide (e.g., a PL polypeptide or PDZ polypeptide) can also be replaced by an amino acid (or peptidomimetic residue) of the opposite chirality. Thus, any amino acid naturally-occurring in the L-configuration (which can also be referred to as the R or S, depending upon the structure of the chemical entity) can be replaced with the amino acid of the same chemical structural type or a peptidomimetic, but of the opposite

chirality, generally referred to as the D- amino acid, but which can additionally be referred to as the R- or S- form.

The mimetics of the invention can also include compositions that contain a structural mimetic residue, particularly a residue that induces or mimics secondary structures, such as a beta turn, beta sheet, alpha helix structures, gamma turns, and the like. For example, substitution of natural amino acid residues with D-amino acids; N-alpha-methyl amino acids; C-alpha-methyl amino acids; or dehydroamino acids within a peptide can induce or stabilize beta turns, gamma turns, beta sheets or alpha helix conformations. Beta turn mimetic structures have been described, e.g., by Nagai, (1985); Feigl (1986);Kahn (1988); Kemp (1988); Kahn (1988a). Beta sheet mimetic structures have been described, e.g., by Smith (1992). For example, a type VI beta turn induced by a cis amide surrogate, 1,5-disubstituted tetrazol, is described by Beusen (1995). Incorporation of achiral omega-amino acid residues to generate polymethylene units as a substitution for amide bonds is described by Banerjee (1996). Secondary structures of polypeptides can be analyzed by, e.g., high-field 1H NMR or 2D NMR spectroscopy, see, e.g., Higgins (1997). See also, Hruby (1997) and Balaji et al., U.S. Pat. No. 5,612,895.

As used herein, "peptide variants" and "conservative amino acid substitutions" refer to peptides that differ from a reference peptide (e.g., a peptide having the sequence of the carboxy-terminus of a specified PL protein) by substitution of an amino acid residue having similar properties (based on size, polarity, hydrophobicity, and the like). Thus, insofar as the compounds that are encompassed within the scope of the invention are partially defined in terms of amino acid residues of designated classes, the amino acids may be generally categorized into three main classes: hydrophilic amino acids, hydrophobic amino acids and cysteine-like amino acids, depending primarily on the characteristics of the amino acid side chain. These main classes may be further divided into subclasses. Hydrophilic amino acids include amino acids having acidic, basic or polar side chains and hydrophobic amino acids include amino acids having aromatic or apolar side chains. Apolar amino acids may be further subdivided to include, among others, aliphatic amino acids. The definitions of the classes of amino acids as used herein are as follows:

"Hydrophobic Amino Acid" refers to an amino acid having a side chain that is uncharged at physiological pH and that is repelled by aqueous solution. Examples of genetically encoded hydrophobic amino acids include Ile, Leu and Val. Examples of non-genetically encoded hydrophobic amino acids include t-BuA.

“Aromatic Amino Acid” refers to a hydrophobic amino acid having a side chain containing at least one ring having a conjugated π -electron system (aromatic group). The aromatic group may be further substituted with groups such as alkyl, alkenyl, alkynyl, hydroxyl, sulfanyl, nitro and amino groups, as well as others. Examples of genetically encoded aromatic amino acids include Phe, Tyr and Trp. Commonly encountered non-genetically encoded aromatic amino acids include phenylglycine, 2-naphthylalanine, β -2-thienylalanine, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 4-chloro-phenylalanine, 2-fluorophenyl-alanine, 3-fluorophenylalanine and 4-fluorophenylalanine.

“Apolar Amino Acid” refers to a hydrophobic amino acid having a side chain that is generally uncharged at physiological pH and that is not polar. Examples of genetically encoded apolar amino acids include Gly, Pro and Met. Examples of non-encoded apolar amino acids include Cha.

“Aliphatic Amino Acid” refers to an apolar amino acid having a saturated or unsaturated straight chain, branched or cyclic hydrocarbon side chain. Examples of genetically encoded aliphatic amino acids include Ala, Leu, Val and Ile. Examples of non-encoded aliphatic amino acids include Nle.

“Hydrophilic Amino Acid” refers to an amino acid having a side chain that is attracted by aqueous solution. Examples of genetically encoded hydrophilic amino acids include Ser and Lys. Examples of non-encoded hydrophilic amino acids include Cit and hCys.

“Acidic Amino Acid” refers to a hydrophilic amino acid having a side chain pK value of less than 7. Acidic amino acids typically have negatively charged side chains at physiological pH due to loss of a hydrogen ion. Examples of genetically encoded acidic amino acids include Asp and Glu.

“Basic Amino Acid” refers to a hydrophilic amino acid having a side chain pK value of greater than 7. Basic amino acids typically have positively charged side chains at physiological pH due to association with hydronium ion. Examples of genetically encoded basic amino acids include Arg, Lys and His. Examples of non-genetically encoded basic amino acids include the non-cyclic amino acids ornithine, 2,3-diaminopropionic acid, 2,4-diaminobutyric acid and homoarginine.

“Polar Amino Acid” refers to a hydrophilic amino acid having a side chain that is uncharged at physiological pH, but which has a bond in which the pair of electrons shared in common by two atoms is held more closely by one of the atoms. Examples of genetically

encoded polar amino acids include Asx and Glx. Examples of non-genetically encoded polar amino acids include citrulline, N-acetyl lysine and methionine sulfoxide.

"Cysteine-Like Amino Acid" refers to an amino acid having a side chain capable of forming a covalent linkage with a side chain of another amino acid residue, such as a disulfide linkage. Typically, cysteine-like amino acids generally have a side chain containing at least one thiol (SH) group. Examples of genetically encoded cysteine-like amino acids include Cys. Examples of non-genetically encoded cysteine-like amino acids include homocysteine and penicillamine.

As will be appreciated by those having skill in the art, the above classification are not absolute, and several amino acids exhibit more than one characteristic property, and can therefore be included in more than one category. For example, tyrosine has both an aromatic ring and a polar hydroxyl group. Thus, tyrosine has dual properties and can be included in both the aromatic and polar categories. Similarly, in addition to being able to form disulfide linkages, cysteine also has apolar character. Thus, while not strictly classified as a hydrophobic or apolar amino acid, in many instances cysteine can be used to confer hydrophobicity to a peptide.

Certain commonly encountered amino acids which are not genetically encoded of which the peptides and peptide analogues of the invention may be composed include, but are not limited to, β -alanine (b-Ala) and other omega-amino acids such as 3-aminopropionic acid (Dap), 2,3-diaminopropionic acid (Dpr), 4-aminobutyric acid and so forth; α -aminoisobutyric acid (Aib); ϵ -aminohexanoic acid (Aha); Δ -aminovaleric acid (Ava); N-methylglycine or sarcosine (MeGly); ornithine (Orn); citrulline (Cit); t-butylalanine (t-BuA); t-butylglycine (t-BuG); N-methylisoleucine (Melle); phenylglycine (Phg); cyclohexylalanine (Cha); norleucine (Nle); 2-naphthylalanine (2-Nal); 4-chlorophenylalanine (Phe(4-Cl)); 2-fluorophenylalanine (Phe(2-F)); 3-fluorophenylalanine (Phe(3-F)); 4-fluorophenylalanine (Phe(4-F)); penicillamine (Pen); 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic); β -2-thienylalanine (Thi); methionine sulfoxide (MSO); homoarginine (hArg); N-acetyl lysine (AcLys); 2,3-diaminobutyric acid (Dab); 2,3-diaminobutyric acid (Dbu); p-aminophenylalanine (Phe(pNH₂)); N-methyl valine (MeVal); homocysteine (hCys) and homoserine (hSer). These amino acids also fall conveniently into the categories defined above.

The classifications of the above-described genetically encoded and non-encoded amino acids are summarized in Table 1, below. It is to be understood that Table 1 is for

- illustrative purposes only and does not purport to be an exhaustive list of amino acid residues which may comprise the peptides and peptide analogues described herein. Other amino acid residues which are useful for making the peptides and peptide analogues described herein can be found, e.g., in Fasman, 1989, CRC Practical Handbook of Biochemistry and Molecular
- 5 Biology, CRC Press, Inc., and the references cited therein. Amino acids not specifically mentioned herein can be conveniently classified into the above-described categories on the basis of known behavior and/or their characteristic chemical and/or physical properties as compared with amino acids specifically identified.

Table 1

Classification	Genetically Encoded	Genetically Non-Encoded
Hydrophobic		
Aromatic	F, Y, W	Phg, Nal, Thi, Tic, Phe(4-Cl), Phe(2-F), Phe(3-F), Phe(4-F), Pyridyl Ala, Benzothienyl Ala
Apolar	M, G, P	
Aliphatic	A, V, L, I	t-BuA, t-BuG, Melle, Nle, MeVal, Cha, bAla, MeGly, Aib
Hydrophilic		
Acidic	D, E	
Basic	H, K, R	Dpr, Orn, hArg, Phe(p-NH ₂), DBU, A ₂ BU
Polar	Q, N, S, T, Y	Cit, AcLys, MSO, hSer
Cysteine-Like	C	Pen, hCys, p-methyl Cys

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- Cyclic derivatives of the peptides of the invention are also part of the present invention. Cyclization may allow the peptide to assume a more favorable conformation for association with molecules in complexes of the invention. Cyclization may be achieved using techniques known in the art, e.g., disulfide bonds may be formed between two appropriately
- 15 spaced components having free sulfhydryl groups, or an amide bond may be formed between an amino group of one component and a carboxyl group of another component. Cyclization may also be achieved using an azobenzene-containing amino acid as described by Ulysse et al.(1995). The side chains of tyrosine and asparagine may be linked to form cyclic peptides.

The components that form the bonds may be side chains of amino acids, non-amino acid components or a combination of the two. In an embodiment of the invention, cyclic peptides are contemplated that have a beta-turn in the right position. Beta-turns may be introduced into the peptides of the invention by adding the amino acids proline and glycine at the right position.

In addition to novel peptides herein disclosed, some peptide sequences that bind to PDZ domains of interest have been previously disclosed, e.g., sequences SEQ ID NO: 173 through SEQ ID NO: 188 are disclosed in WO02311512, incorporated herein by reference, wherein the sequences bind to RIM2 and other PDZ domains, and SEQ ID NO: 189 and SEQ ID NO: 190 are disclosed in WO03014303, incorporated herein by reference, wherein the sequences bind to RIM2 and other PDZ domains binding sequences.

In some embodiments, the agent that inhibits MUC1 binding to a PDZ domain is a peptide of the formula $X^1\text{-aa}^2\text{-aa}^1\text{-aa}^0$ wherein aa^0 is a hydrophobic aliphatic amino acid residue or a hydrophobic aromatic amino acid residue, aa^2 is a hydrophobic aliphatic amino acid residue, hydrophobic aromatic amino acid residue, polar amino acid residue, basic amino acid residue or an acidic amino acid residue, aa^1 is an amino acid residue and X^1 is a sequence of 0 to 200 amino acid residues, or 0 to 100 amino acid residues, or 0 to 50 amino acid residues, or 0 to 25 amino acid residues. In some embodiments, X^1 is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 amino acid residues. In some embodiments aa^0 is V, L, A, I, S or Y and aa^2 is V, L, A, I, F, Y, W, Q, N, S, T, R, K, D or E. In some embodiments, the residues $\text{aa}^2\text{-aa}^1\text{-aa}^0$ of the peptide of the formula $X^1\text{-aa}^2\text{-aa}^1\text{-aa}^0$ is selected from SEQ ID NO: 1 through SEQ ID NO: 40: RIV (SEQ ID NO: 1); LYI (SEQ ID NO: 2); SVV (SEQ ID NO: 3); AEV (SEQ ID NO: 4); SQL (SEQ ID NO: 5); SAA (SEQ ID NO: 6); SDA (SEQ ID NO: 7); SLV (SEQ ID NO: 8); SGI (SEQ ID NO: 9); SKV (SEQ ID NO: 10); FYA (SEQ ID NO: 11); TRV (SEQ ID NO: 12); TTL (SEQ ID NO: 13); TDV (SEQ ID NO: 14); SDV (SEQ ID NO: 15); YFI (SEQ ID NO: 16); YYV (SEQ ID NO: 17); ELV (SEQ ID NO: 18); IWA (SEQ ID NO: 19); ANL (SEQ ID NO: 20); IIA (SEQ ID NO: 21); RIA (SEQ ID NO: 22); YWA (SEQ ID NO: 23); IWS (SEQ ID NO: 24); INL (SEQ ID NO: 25); IRV (SEQ ID NO: 26); VEV (SEQ ID NO: 27); YIV (SEQ ID NO: 28); YQI (SEQ ID NO: 29); LML (SEQ ID NO: 30); VPV (SEQ ID NO: 31); IVL (SEQ ID NO: 32); VSL (SEQ ID NO: 33); VWV (SEQ ID NO: 34); EYV (SEQ ID NO: 35); EIV (SEQ ID NO: 36); IY (SEQ ID NO: 37); KIV (SEQ ID NO: 38); TWV (SEQ ID NO: 39); and TQV (SEQ ID NO: 40).

In some embodiments, the peptide of formula $X^1\text{-aa}^2\text{-aa}^1\text{-aa}^0$ comprises as the carboxy-terminus the carboxy-terminal 4, 5, 6, 7, 8 or 9 residues of a nine amino acid residue

sequence selected from SEQ ID NO: 41 through SEQ ID NO: 94: ARGDRKRIV (SEQ ID NO: 41); TLASHQLYI (SEQ ID NO: 42); GMTSSSSVV (SEQ ID NO: 43); YGSPRYAEV (SEQ ID NO: 44); WPPSSSSQL (SEQ ID NO: 45); DDYDDISAA (SEQ ID NO: 46); LKPPATSDA (SEQ ID NO: 47); DKERLTSDA (SEQ ID NO: 48); FRNETQSLV (SEQ ID NO: 49); ALRASEGI (SEQ ID NO: 50); LVBAQKSKV (SEQ ID NO: 51); PTKQEEFYA (SEQ ID NO: 52); FSRRPKTRV (SEQ ID NO: 53); SSGHTSTTL (SEQ ID NO: 54); NIKKIPTDV (SEQ ID NO: 55); KMDSIESDV (SEQ ID NO: 56); DSSRKEYFI (SEQ ID NO: 57); KNKDKEYYV (SEQ ID NO: 58); VTDHKTELIV (SEQ ID NO: 59); QDEEEGIWA (SEQ ID NO: 60); AVAATSINL (SEQ ID NO: 61); AVAATYSINL (SEQ ID NO: 62); ARGDRKRWA (SEQ ID NO: 63); ARGDRKRWL (SEQ ID NO: 64); AVAATGIWA (SEQ ID NO: 65); QDEEETIWA (SEQ ID NO: 66); ARSDRTIWA (SEQ ID NO: 67); ARSDRTIA (SEQ ID NO: 68); ARSDRKRIA (SEQ ID NO: 69); SRTDRKYWA (SEQ ID NO: 70); QDEEEGIWS (SEQ ID NO: 71); SRTVRKIWA (SEQ ID NO: 72); SVTSTINL (SEQ ID NO: 73); ARGDRKIRV (SEQ ID NO: 74); ARTDRKVEV (SEQ ID NO: 75); ARGDRKYIV (SEQ ID NO: 76); SRTDRKYQI (SEQ ID NO: 77); ARGDVRLML (SEQ ID NO: 78); ARGDRKVPV (SEQ ID NO: 79); QDERRLIVL (SEQ ID NO: 80); ARGDRLVSL (SEQ ID NO: 81); ARGIRLVWV (SEQ ID NO: 82); ARGDRYRIV (SEQ ID NO: 83); SRTDRLEYV (SEQ ID NO: 84); ARGDRLEIV (SEQ ID NO: 85); ARGDRITLY (SEQ ID NO: 86); ARGDRRRIV (SEQ ID NO: 87); ARGDRKKIV (SEQ ID NO: 88); ARSDRKIRV (SEQ ID NO: 89); KNKDKEYYV (SEQ ID NO: 90); GMTSSSSVV (SEQ ID NO: 91); ARGRRRETWV (SEQ ID NO: 92); QDRVETRV (SEQ ID NO: 93); and LQRRRETQV (SEQ ID NO: 94).

In some embodiments, the peptide of formula $X^1\text{-aa}^2\text{-aa}^1\text{-aa}^0$ comprises as the carboxy- terminus the carboxy-terminal 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 amino acid residues of NGGSSLSYTNPAVAAASANL (SEQ ID NO: 95) or NGGSSLSYTNPAVAATSANL (SEQ ID NO: 96).

In some embodiments, the amino-terminus of X^1 comprises $X^2\text{-X}^3$, wherein X^2 is a transmembrane transporter peptide sequence and X^3 is an optional linker sequence. In some embodiments, the transmembrane transporter peptide sequence is derived from the *Drosophila* antennapedia protein, or homologs thereof. The 60 amino acid long homeodomain of the homeo-protein antennapedia has been demonstrated to translocate through biological membranes and can facilitate the translocation of coupled peptides. See for example Derossi et al. (1994) and Perez et al. (1992). It has been demonstrated that fragments as small as 16 amino acids long of this protein are sufficient to drive internalization.

Examples of transmembrane transporter peptide sequences derived in unmodified or modified form from antennapedia include: RQKIWFQNRRMKWKK (SEQ ID NO: 97) (Derossi et al., 1994); SGRQKIWFQNRRMKWKKC (SEQ ID NO: 98) (Console et al., 2003); RRWRRWRRWRRWRR (SEQ ID NO: 99) (Williams et al., 1997);

5 KKWKMRNRFWIKIQR (SEQ ID NO: 100) (Derossi et al., 1996); and KKWKMRNRFWIKIQR (SEQ ID NO: 101) (Pescarolo et al., 2001). The present invention contemplates a PDZ inhibitory peptide or peptidomimetic sequence as described herein, and at least a portion of the Antennapedia protein (or homolog thereof) sufficient to increase the transmembrane transport of the chimeric protein, relative to the PDZ inhibitory

10 peptide or peptidomimetic, by a statistically significant amount.

Another example of an internalizing peptide is the HIV transactivator (TAT) protein. This protein appears to be divided into four domains (Kuppuswamy et al., 1989). Purified TAT protein is taken up by cells in tissue culture (Frankel and Pabo, 1989), and peptides, such as the fragment corresponding to residues 37-62 of TAT, are rapidly taken up by cell

15 *in vitro* (Green and Loewenstein, 1989). The highly basic region mediates internalization and targeting of the internalizing moiety to the nucleus (Ruben et al., 1989). Examples of transmembrane transporter peptide sequences derived in unmodified or modified form from TAT include YGRKKRRQRRR (SEQ ID NO: 102) (Vives et al., 1997); GRKRRQRRPPQ (SEQ ID NO: 103) (all L or all D amino acids) (Futaki et al., 2001);

20 SGYGRKKRRQRRRC (SEQ ID NO: 104) (Console et al., 2003); RRRQRRKKRGY (SEQ ID NO: 105) (D amino acids) (Snyder et al., 2004); YARAAARQARA (SEQ ID NO: 106) (Ho et al., 2001); RKKRRQRRR (SEQ ID NO: 107) (Wender et al., 2000); RRRRRRRR (SEQ ID NO: 108) (using either all L or all D amino acids) (Wender et al., 2000); RRRRRR (SEQ ID NO: 109) (Futaki et al., 2001); RRRRRRRR (SEQ ID NO: 110) (Futaki et al.,

25 2001); and RRRQRR (SEQ ID NO: 111) (all D amino acids) (WO03059942). In some embodiments the peptide of formula $X^1\text{-aa}^2\text{-aa}^1\text{-aa}^0$ comprising a TAT transmembrane transporter peptide sequence selected from SEQ ID NO: 134 through 172.

Transmembrane transporter peptide sequences such as those derived from TAT and Antennapedia protein can also be attached to liposomes and the PDZ inhibitory peptide is

30 translocated within the liposome (Torchilin & Levchenko, 2003; Tseng et al., 2002)

Other transmembrane transporter peptide sequences include galanin and mastoparan chimera sequences, e.g., GWTLNSAGYLLGKINLKALAALAKKIL (SEQ ID NO: 112) (Pooga et al., 1998) and AGYLLGKINLKALAALAKKIL (SEQ ID NO: 113) (Soomets et al., 2000); Herpes Simplex Virus VP22 derived sequences, e.g.,

- DAATATRGRSAASRPTRPRAPARSASRRRVE (SEQ ID NO: 114) (Elliot & O'Hare, 1997) and GALFLGFLGAAGSTMGAWSQPKSKRKV (SEQ ID NO: 115) (Morris et al., 1997); pegelin derived sequences, e.g., RGRSLYSRRRFSTSTGR (SEQ ID NO:116) (Rousselle et al., 2000); integrin $\beta 3$ signal derived sequences, e.g.,
- 5 VTVVLALGALAGVGVG (SEQ ID NO:117) (Lin et al., 1996); Kaposi FGF signal derived sequences, e.g., AAVALLPAVLLALLAP (SEQ ID NO: 118) (Lin et al., 1996); amphipathic peptide sequences, e.g., KLALKLALKALKAAKLKLA (SEQ ID NO: 119) (Oehlke et al., 1998), FHV coat derived sequences, e.g., RRRNRTRRRNRVR (SEQ ID NO: 120) (Suzuki et al., 2002); synthetic sequences, e.g., PIRRRKKLRRLK (SEQ ID NO: 121) and
- 10 RRQRRTSKLMKR (SEQ ID NO: 122) (Mi et al., 2000); VE cadherin derived sequences, e.g., LLILRRRIKQAHASK (SEQ ID NO: 123) (Blmquist et al., 2001) and nuclear localization signal derived sequences, e.g., SV40-NLS PKKKRKV (SEQ ID NO: 124) and Nucleoplasmin-NLS KRPAIKKAGQAKKKK (SEQ ID NO: 125) (Futaki et al., 2001).

- While not wishing to be bound by any particular theory, it is noted that hydrophilic
- 15 polypeptides may be also be physiologically transported across the membrane barriers by coupling or conjugating the polypeptide to a transportable peptide which is capable of crossing the membrane by receptor-mediated transcytosis. Suitable internalizing peptides of this type can be generated using all or a portion of, e.g., a histone, insulin, transferrin, basic albumin, prolactin and insulin-like growth factor I (IGF-I), insulin-like growth factor II (IGF-
- 20 II) or other growth factors. For instance, it has been found that an insulin fragment, showing affinity for the insulin receptor on capillary cells, and being less effective than insulin in blood sugar reduction, is capable of transmembrane transport by receptor-mediated transcytosis and can therefore serve as an internalizing peptide for the subject transcellular peptides and peptidomimetics. Preferred growth factor-derived internalizing peptides include
- 25 EGF (epidermal growth factor)-derived peptides, such as CMHESLDSYTC (SEQ ID NO: 126) and CMYTEALDKYAC (SEQ ID NO: 127); TGF- β (transforming growth factor beta)-derived peptides; peptides derived from PDGF (platelet-derived growth factor) or PDGF-2; peptides derived from IGF-I (insulin-like growth factor) or IGF-II; and FGF (fibroblast growth factor)-derived peptides. Also included are antibodies to receptors that are
- 30 internalized upon binding of the antibody. Such antibodies include, but are not limited to, those that target MUC1, MUC4, EGFR, ErbB2, c-Met, GM-CSF alpha and beta receptors, bFGF receptors, TNF receptors, TGF beta receptor I-III, estrogen receptors, and G-protein coupled receptors.

Another class of translocating/internalizing peptides exhibits pH-dependent membrane binding. For an internalizing peptide that assumes a helical conformation at an acidic pH, the internalizing peptide acquires the property of amphiphilicity, e.g., it has both hydrophobic and hydrophilic interfaces. More specifically, within a pH range of approximately 5.0-5.5, an internalizing peptide forms an alpha-helical, amphiphilic structure that facilitates insertion of the moiety into a target membrane. An alpha-helix-inducing acidic pH environment may be found, for example, in the low pH environment present within cellular endosomes. Such internalizing peptides can be used to facilitate transport of PDZ inhibitory peptides and peptidomimetics, taken up by an endocytic mechanism, from endosomal compartments to the cytoplasm.

A preferred pH-dependent membrane-binding internalizing peptide includes a high percentage of helix-forming residues, such as glutamate, methionine, alanine and leucine. In addition, a preferred internalizing peptide sequence includes ionizable residues having pKa's within the range of pH 5-7, so that a sufficient uncharged membrane-binding domain will be present within the peptide at pH 5 to allow insertion into the target cell membrane.

Another preferred pH-dependent membrane-binding internalizing peptide in this regard is aa1-aa2-aa3-EAALA(BALA)4-EALEALAA-amide, which represents a modification of the peptide sequence of Subbarao et al. (1987). Within this peptide sequence, the first amino acid residue (aa1) is preferably a unique residue, such as C or K, that facilitates chemical conjugation of the internalizing peptide to a targeting protein conjugate. Amino acid residues 2-3 may be selected to modulate the affinity of the internalizing peptide for different membranes. For instance, if both residues 2 and 3 are K or R, the internalizing peptide will have the capacity to bind to membranes or patches of lipids having a negative surface charge. If residues 2-3 are neutral amino acids, the internalizing peptide will insert into neutral membranes.

Yet other preferred internalizing peptides include peptides of apo-lipoprotein A-1 and B; peptide toxins, such as melittin, bombolitin, delta hemolysin and the pardaxins; antibiotic peptides, such as alamethicin; peptide hormones, such as calcitonin, corticotrophin releasing factor, beta endorphin, glucagon, parathyroid hormone, pancreatic polypeptide; and peptides corresponding to signal sequences of numerous secreted proteins. In addition, exemplary internalizing peptides may be modified through attachment of substituents that enhance the alpha-helical character of the internalizing peptide at acidic pH.

Yet another class of internalizing peptides suitable for use within the present invention includes hydrophobic domains that are "hidden" at physiological pH, but are exposed in the

low pH environment of the target cell endosome. Upon pH-induced unfolding and exposure of the hydrophobic domain, the moiety binds to lipid bilayers and effects translocation of the covalently linked polypeptide into the cell cytoplasm. Such internalizing peptides may be modeled after sequences identified in, e.g., *Pseudomonas* exotoxin A, clathrin, or Diphtheria toxin.

Pore-forming proteins or peptides may also serve as internalizing peptides herein. Pore-forming proteins or peptides may be obtained or derived from, for example, C9 complement protein, cytolytic T-cell molecules or NK-cell molecules. These moieties are capable of forming ring-like structures in membranes, thereby allowing transport of attached polypeptide through the membrane and into the cell interior.

Mere membrane intercalation of an internalizing peptide may be sufficient for translocation of the PDZ inhibitory peptide or peptidomimetic, across cell membranes. However, translocation may be improved by attaching to the internalizing peptide a substrate for intracellular enzymes (i.e., an "accessory peptide"). It is preferred that an accessory peptide be attached to a portion(s) of the internalizing peptide that protrudes through the cell membrane to the cytoplasmic face. The accessory peptide may be advantageously attached to one terminus of a translocating/internalizing moiety or anchoring peptide. An accessory moiety of the present invention may contain one or more amino acid residues. In one embodiment, an accessory moiety may provide a substrate for cellular phosphorylation (for instance, the accessory peptide may contain a tyrosine residue).

In embodiments wherein the amino terminus of X^1 comprises X^2 - X^3 , X^3 , the optional linker X^3 may be any suitable flexible polylinker, including GGGGS (SEQ ID NO: 128) repeated 1 to 3 times (Huston et al., 1988); EGKSSGSGSESKVD (SEQ ID NO: 129) (Chaudhary et al., 1990); KBGSGVSSEQLAQFRSLD (SEQ ID NO: 130) (Bird et al., 1988).

In some embodiments, the peptide of the formula X^1 -aa²-aa¹-aa⁰ is a peptide of the formula X^1 -aa³-aa⁷-aa⁶-aa²-aa⁴-aa³-aa²-aa¹-aa⁰, wherein X^1 is as defined previously and wherein in some embodiments is a peptide of the formula X^2 -aa⁸-aa⁷-aa⁶-aa⁵-aa⁴-aa³-aa²-aa¹-aa⁰, wherein, as defined previously, X^2 is a transmembrane transporter sequence, which in some embodiments is selected from SEQ ID NO: 95 through SEQ ID NO: 127, which in some embodiments is SEQ ID NO: 98, SEQ ID NO: 104 or SEQ ID NO: 119. In some embodiments aa¹ is a hydrophobic aromatic amino acid residue, which may be W or Y. In some embodiments aa⁴ is a basic amino acid residue or acidic amino acid residue, wherein in some embodiments, the basic amino acid residue is R and in some embodiments the acidic amino acid residue is E. In some embodiments, aa⁷ is an acidic, basic or hydrophobic

aliphatic amino acid residue, wherein in some embodiments the basic amino acid residue is R, the acidic amino acid residue is D, and the hydrophobic aliphatic amino acid residue is V. In some embodiments, the peptide of formula X^4 -aa³-aa⁷-aa⁶-aa⁵-aa⁴-aa³-aa²-aa¹-aa⁰ is SEQ ID NO: 137, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 148, SEQ ID NO: 150, SEQ ID NO: 160, SEQ ID NO: 168, or SEQ ID NO: 170.

One aspect of the present invention encompasses compositions and pharmaceutical compositions of the foregoing described peptides that inhibit the binding of the cytoplasmic domain of MUC1 to one or more PDZ domains.

The polypeptides of the present invention can be created by synthetic techniques or recombinant techniques which employ genomic or cDNA cloning methods. Polypeptides can be routinely synthesized using solid phase or solution phase peptide synthesis. Methods of preparing relatively short polypeptides peptides, by chemical synthesis are well known in the art. Such polypeptides could, for example be produced by solid-phase peptide synthesis techniques using commercially available equipment and reagents such as those available from Milligen (Bedford, Mass.) or Applied Biosystems-Perkin Elmer (Foster City, CA). Alternatively, segments of such polypeptides could be prepared by solid-phase synthesis and linked together using segment condensation methods such as those described by Dawson et al., (1994). During chemical synthesis of such polypeptides, substitution of any amino acid is achieved simply by replacement of the residue that is to be substituted with a different amino acid monomer.

III. Combination with Chemotherapeutic Agents

The present invention encompasses the use of modulators of MUC1 mediated signal transduction of the present invention in combination with chemotherapeutic agents. While not being limited by any particular theory, MUC1 inhibits the apoptotic response to genotoxic stress induced by certain chemotherapeutic agents, and thereby induces resistance to such agents. Modulators of MUC1 mediated signal transduction may be used to mitigate this MUC1 mediated response to chemotherapeutic agents, thereby enhancing the effectiveness of such agents. In this regard, the compositions of the present invention will be useful for the treatment cancer cells resistant to chemotherapeutic agents, including residual cancers remaining or reoccurring after cancer chemotherapy. The foregoing rational also pertains to the combination of compositions of the present invention and ionizing radiation.

The chemotherapeutic agents useful in the methods of the invention include the full spectrum of compositions and compounds which are known to be active in killing and/or

inhibiting the growth of cancer cells. The chemotherapeutic agents, grouped by mechanism of action include DNA-interactive agents, antimetabolites, tubulin interactive agents, anti-hormonals, anti-virals, ODC inhibitors and other cytotoxics such as hydroxy urea. Any of these agents are suitable for use in the methods of the present invention. DNA-interactive agents include the alkylating agents, e.g., cisplatin, cyclophosphamide, altretamine; the DNA strand-breakage agents, such as bleomycin; the intercalating topoisomerase II inhibitors, e.g., dactinomycin and doxorubicin; the nonintercalating topoisomerase II inhibitors such as, etoposide and teniposide; and the DNA minor groove binder plicamycin.

The alkylating agents form covalent chemical adducts with cellular DNA, RNA and protein molecules and with smaller amino acids, glutathione and similar chemicals. Generally, these alkylating agents react with a nucleophilic atom in a cellular constituent, such as an amino, carboxyl, phosphate, sulfhydryl group in nucleic acids, proteins, amino acids, or glutathione. The mechanism and the role of these alkylating agents in cancer therapy is not well understood. Typical alkylating agents include: nitrogen mustards, such as chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, uracil mustard; aziridine such as thiotepea; methanesulphonate esters such as busulfan; nitroso ureas, such as carmustine, lomustine, streptozocin; platinum complexes such as cisplatin, carboplatin; bioreductive alkylators, such as mitomycin and procabazine, dacarbazine and altretamine; DNA strand-breaking agents including bleomycin.

Topoisomerases are ubiquitous cellular enzymes which initiate transient DNA strand breaks during replication to allow for free rotation of the strands. The functionality of these enzymes is critical to the replication process of DNA. Without them, the torsional strain in the DNA helix prohibits free rotation, the DNA strands are unable to separate properly, and the cell eventually dies without dividing. Topo I links to the 3'-terminus of a DNA single strand break, while Topo II links to the 5'-terminus of a double strand DNA break. DNA topoisomerase II inhibitors include intercalators such as amsacrine, dactinomycin, daunorubicin, doxorubicin, idarubicin and mitoxantrone; nonintercalators such as etoposide and teniposide; camptothecins including irinotecan (CPT-II) and topotecan. A representative DNA minor groove binder is plicamycin.

The antimetabolites generally exert cytotoxic activity by interfering with the production of nucleic acids by one or the other of two major mechanisms. Some of the drugs inhibit production of the deoxyribonucleoside triphosphates that are the immediate precursors of DNA synthesis, thus inhibiting DNA replication. Some of the compounds are sufficiently like purines or pyrimidines to be able to substitute for them in the anabolic nucleotide

pathways. These analogs can then be substituted into the DNA and RNA instead of their normal counterparts. The antimetabolites useful herein include: folate antagonists such as methotrexate and trimetrexate; pyrimidine antagonists such as fluorouracil, fluorodeoxyuridine, azacitidine, cytarabine, and floxuridine; purine antagonists include mercaptopurine, 6-thioguanine, fludarabine, pentostatin; sugar modified analogs include cytarabine, fludarabine; ribonucleotide reductase inhibitors include hydroxyurea.

Tubulin interactive agents interfere with cell division by binding to specific sites on Tubulin, a protein that polymerizes to form cellular microtubules. Microtubules are critical cell structure units. When the interactive agents bind on the protein, the cell cannot properly form microtubules. Tubulin interactive agents include vincristine and vinblastine, both alkaloids and the taxanes (paclitaxel and docetaxel). Although their mechanisms of action are different, both taxanes and vinca alkaloids exert their biological effects on the cell microtubules. Taxanes act to promote the polymerization of tubulin, a protein subunit of spindle microtubules. The end result is the inhibition of depolymerization of the microtubules, which causes the formation of stable and nonfunctional microtubules. This disrupts the dynamic equilibrium within the microtubule system, and arrests the cell cycle in the late G₂ and M phases, which inhibits cell replication.

Like taxanes, vinca alkaloids also act to affect the microtubule system within the cells. In contrast to taxanes, vinca alkaloids bind to tubulin and inhibit or prevent the polymerization of tubulin subunits into microtubules. Vinca alkaloids also induce the depolymerization of microtubules, which inhibits microtubule assembly and mediates cellular metaphase arrest. Vinca alkaloids also exert effects on nucleic acid and protein synthesis; amino acid, cyclic AMP, and glutathione synthesis; cellular respiration; and exert immunosuppressive activity at higher concentrations.

Antihormonal agents exert cytotoxic activity by blocking hormone action at the end-receptor organ. Several different types of neoplasm require hormonal stimulation to propagate cell reproduction. The antihormonal agents, by blocking hormone action, deprive the neoplastic cells of a necessary stimulus to reproduce. As the cells reach the end of their life cycle, they die normally, without dividing and producing additional malignant cells.

Antihormonal agents are typically derived from natural sources and include: estrogens, conjugated estrogens and ethinyl estradiol and diethylstilbestrol, chlortrianisen and idenestrol; progestins such as hydroxyprogesterone caproate, medroxyprogesterone, and megestrol; androgens such as testosterone, testosterone propionate; fluoxymesterone, methyltestosterone.

Adrenal corticosteroids are derived from natural adrenal cortisol or hydrocortisone. They are used because of their anti-inflammatory benefits as well as the ability of some to inhibit mitotic divisions and to halt DNA synthesis. These compounds include prednisone, dexamethasone, methylprednisolone, and prednisolone.

Leutinizng-releasing hormone agents or gonadotropin-releasing hormone antagonists are used primarily in the treatment of prostate cancer. These include leuprolide acetate and goserelin acetate. They prevent the biosynthesis of steroids in the testes.

Anti-hormonal agents include antiestrogenic agents such as tamoxifen, antiandrogen agents such as flutamide, and antiadrenal agents such as mitotane and aminoglutethimide.

ODC (or ornithine decarboxylase) inhibitors inhibit cancerous and pre-cancerous cell proliferation by depleting or otherwise interfering with the activity of ODC, the rate limiting enzyme of polyamine biosynthesis important to neoplastic cell growth. In particular, polyamine biosynthesis wherein ornithine is converted to the polyamine, putrescine, with putrescine being subsequently by converted to spermidine and spermine appears to be an essential biochemical event in the proliferation of neoplastic growth in a variety of cancers and cancer cell lines and the inhibition of ODC activity or depletion of ODC in such neoplastic cells has been shown to reduce polyamine levels in such cells leading to cell growth arrest; more differentiated cell morphology and even cellular senescence and death. In this regard, ODC or polyamine synthesis inhibitors are considered to be more cytotoxic agents functioning to prevent cancer recurrence or the conversion of pre-cancerous cells to cancerous cells than cytotoxic or cell killing agents. A suitable ODC inhibitor is efornithine or α -difluoromethyl-ornithine, an orally available, irreversible ODC inhibitor, as well as a variety of polyamine analogs which are in various stages of pre-clinical and clinical research.

Other cytotoxics include agents which interfere or block various cellular processes essential for maintenance of cellular functions or cell mitosis as well as agents which promote apoptosis. In this regard, hydroxyurea appears to act via inhibitors of the enzyme ribonucleotide reductase whereas asparaginase enzymatically converts asparagine into non-functional aspartic acid thereby blocking protein synthesis in a tumor.

Compositions of the present invention can also be used in combination with antibodies to HER-2, such as Trastuzumab (Herceptin (H)). In addition, the present invention also encompasses the use of MUC1 domain antagonists in combination with epidermal growth factor receptor-interactive agents such as tyrosine kinase inhibitors. Tyrosine kinase inhibitors suitably include imatinib (Novartis), OSI-774 (OSI Pharmaceuticals), ZD-1839 (AstraZeneca), SU-101 (Sugen) and CP-701 (Cephalon).

When used in the treatment methods of the present invention, it is contemplated that the chemotherapeutic agent of choice can be conveniently used in any formulation which is currently commercially available, and at dosages which fall below or within the approved label usage for single agent use.

IV. Combination with Ionizing Radiation

In the present invention, the term "ionizing radiation" means radiation comprising particles or photons that have sufficient energy or can produce sufficient energy via nuclear interactions to produce ionization (gain or loss of electrons). An exemplary and preferred ionizing radiation is an x-radiation. Means for delivering x-radiation to a target tissue or cell are well known in the art. The amount of ionizing radiation needed in a given cell generally depends on the nature of that cell. Means for determining an effective amount of radiation are well known in the art. Used herein, the term "an effective dose" of ionizing radiation means a dose of ionizing radiation that produces cell damage or death when given in conjunction with the modulators of MUC1 mediated signal transduction of the present invention, optionally further combined with a chemotherapeutic agent.

Dosage ranges for x-rays range from daily doses of 50 to 200 roentgens for prolonged periods of time (3 to 4 weeks), to single doses of 2000 to 6000 roentgens. Dosage ranges for radioisotopes vary widely, and depend on the half-life of the isotope, the strength and type of radiation emitted, and the uptake by the neoplastic cells.

Any suitable means for delivering radiation to a tissue may be employed in the present invention, in addition to external means. For example, radiation may be delivered by first providing a radiolabeled antibody that immunoreacts with an antigen of the tumor, followed by delivering an effective amount of the radiolabeled antibody to the tumor. In addition, radioisotopes may be used to deliver ionizing radiation to a tissue or cell.

V. Formulations

The compositions of the present invention such as peptides can be formulated in a variety of conventional pharmaceutical formulations and administered to cancer patients, in need of treatment, by any one of the drug administration routes conventionally employed including oral, intravenous, intraarterial, parental or intraperitoneal.

For oral administration the compositions of the present invention may be formulated, for example, with an inert diluent or with an assimilable edible carrier, or enclosed in hard or soft shell gelatin capsules, or compressed into tablets, or incorporated directly with the food

of the diet. For oral therapeutic administration, the active compound may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of the unit. The amount of active compounds in such therapeutically useful compositions is such that a suitable dosage will be obtained.

The tablets, troches, pills, capsules and the like may also contain the following: a binder, a gum tragacanth, acacia, cornstarch, or gelatin; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit for is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compounds sucrose as a sweetening agent methyl and propylparabens as preservatives, a dye and flavoring, such as cherry or orange flavor. Of course, any material used in preparing a dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, other chemotherapeutic compounds may be incorporated into sustained-release preparation and formulations.

Pharmaceutical formulations of the compositions of the present invention that are suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the compositions of the present invention in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the composition.

VI. Treatment Methods

Tumors that can be suitably treated with the methods of the present invention include; but are not limited to, tumors of the brain (glioblastomas, medulloblastoma, astrocytoma, oligodendroglioma, ependymomas), lung, liver, spleen, kidney, lymph node, small intestine, pancreas, blood cells, colon, stomach, breast, endometrium, prostate, testicle, ovary, skin, head and neck, esophagus, bone marrow, blood and other tissue. The tumor may be distinguished as metastatic and non-metastatic. Pre-malignant lesions may also be suitably treated with the methods of the present invention.

The treatment with modulators of compositions of the present invention may precede or follow irradiation and/or chemotherapy by intervals ranging from seconds to weeks and/or be administered concurrently with such treatments. In embodiments where the compositions of the present invention and irradiation and/or chemotherapy are applied separately to the cell, steps should be taken to ensure that a significant period of time does not expire between the time of each delivery, such that the combination of the two or three treatments would still be able to exert an advantageously combined effect on the cell. In such instances, it is contemplated that one would contact the cell with the treatment agents or modalities within amount 0.1 to 25 h of each other and, more preferably, within about 1 to 4 h of each other,

with a delay time of only about 1 h to about 2 h being most preferred. In some situations, it is desirable to extend the time period of treatment significantly, however, where several days (2, 3, 4, 5, 6 or 7) or several weeks (1, 2, 3, 4, 5, 6, 7 or 8) lapse between the respective administrations. In any case, the invention contemplates that the compositions of the present invention may be given before, after or even simultaneously with the ionizing radiation and/or chemotherapeutic agent.

In the methods of the present invention, the actual dosage of compositions of the present invention employed will depend on a variety of factors including the type and severity of cancer being treated, and the additive or synergistic treatment effects of the compositions of the present invention and the other treatment modality or modalities selected.

VII. Screening Methods

One aspect of the present invention is the use of screening methodologies, including high-throughput screens, related to the identification of compounds that modulate the binding of MUC1-CD to PDZ domains. Some embodiments utilize Omi/HtrA2, a MUC1-CD PDZ domain containing protein with serine protease activity that inhibits CIAP1, which is one of at least five human inhibitors of apoptosis (IAP) (Deveraux & Reed, 1999). The inhibition of CIAP1 is caused by cleavage at one of at least two sites, i.e., between amino acid residues 90 and 91 or 130 and 131 (numbering as per GenBank ND_001157[gi:4502417] (Jin et al., 2003). The immediate amino acid residues adjacent to the cleavage points (denoted by ^V) are: GLML^VDNWK with L and D corresponding to amino acid residues 90 and 91, and NTSP^VMRNS with P and M corresponding to amino acid residues 130 and 131. These and related peptides, such as 7-mers, 6-mers, 5-mers, 4-mers, and the like, may be used as model substrates in assays quantifying HtrA2 serine protease activity.

In some embodiments of the present invention, the aforementioned CIAP1 derived sequences are utilized in a homogeneous time-resolved fluorescence quenching assay (TR-FQA). The principal of such an assay is the use of a peptide substrate with a fluorescent tag, usually a europium chelate (e.g., LANCE, PerkinElmer Life and Analytical Sciences, Boston MA) coupled to one end and a quencher of the fluorescence, e.g., dabcyl, coupled to the other end. Upon cleavage of the peptide, the quencher will be separated and a time-resolved fluorescent signal is generated and quantified (see e.g., Karvinen et al., 2002, herein incorporated by reference). The peptides can be synthesized by standard FMOC chemistry (e.g., Applied Biosystems 433A peptide synthesizer, Foster City, CA). The building block

for dabcyI is available from Molecular Probes (Eugene, OR), and is used to prepare an intermediate peptide e.g., aminohexyl-LMLDNW-dabcyI-aminohexyl. The peptide intermediate is then labeled with the fluorescent europium chelate W1024 (PerkinElmer Life and Analytical Sciences, Boston MA). Peptide substrates are purified by conventional methods such as HPLC. Thus, one aspect of the present invention are substrate peptides: X^1 - X^2 -LD- X^3 - X^4 , wherein X^1 is a fluorescent label, which may be a europium chelate, which may be a europium isothiocyanate chelate, which may be W1024, X^2 is GLM, LM or M, X^3 is DNW, DN or D and X^4 is a dabcyI quenching group, or X^1 - X^5 -PM- X^6 - X^4 , wherein X^1 and X^4 are as described previously and X^5 is NTS, TS or S and X^6 is MRN, MR or M.

The foregoing substrates may be used to measure the activity of HtrA2, which may be a purified recombinant HtrA2. The full length human HtrA2 clone is available from the IMAGE consortium (GenBak AI979237[gi:5804267]). GST fusion proteins may be used, the preparation and purification of such having been disclosed by Faccio et al. (2000), herein incorporated by reference. GST-HtrA2 fusion proteins may be attached to microbeads by methods known in the art. The assays may be undertaken in multi-well plates and time resolved fluorescence measured by suitable detector means such as a VICTOR V multilabel counter or a ViewLux ultra-HTS microplate imager (PerkinElmer Life and Analytical Sciences, Boston MA). An alternative method using agarose sheets instead of multi-well plates has been described for Caspase-3 and may be adapted for HtrA2 (Sujatha et al., 2002, herein incorporated by reference).

HtrA2 promotes apoptosis (Martins, 2002) while MUC1 prevents apoptosis. Thus binding of MUC1 to the PDZ domain of HtrA2 should decrease the serine protease activity and consequently inhibit the ability of HtrA2 to inactivate CIAP1. Addition of MUC1-CD to the assay will therefore inhibit the time resolved fluorescent signal. This system can be used as a high-throughput-screen to select compounds for the ability to inhibit the MUC1-CD binding to the HtrA2 PDZ domain as indicated by the increase in the time resolved fluorescent signal.

EXAMPLES OF THE INVENTION

Example 1: Requirement for Carboxy-terminal Amino Acids for Co-localization of MUC1 with FGFR3

293 cells were transiently transfected with pIRESpuro2-Flag-MUC1-CD(1-72) or pIRESpuro2-Flag-MUC1-CD(1-68) that respectively expressed a full length MUC1 cytoplasmic domain:

CQCRRKNYGQLDIFPARDTYHPMSEYPTYHITHGRYVPPSSIDRSPYEKVSAG
 NGGSSLSYTNPAVAATSANL (SEQ ID NO: 131) or a truncated domain formed by
 deletion of the four carboxy-terminal amino acids:

CQCRRKNYGQLDIFPARDTYHPMSEYPTYHITHGRYVPPSSIDRSPYEKVSAG

- 5 NGGSSLSYTNPAVAAT (SEQ ID NO: 132).

Cell lysates were prepared from subconfluent cells as described by Li et al. (1998).
 Equal amounts of cell lysate were incubated with anti-FGFR3 or mouse IgG. The immune
 complexes were prepared as described by Li et al. (1998), separated by SDS-PAGE and
 transferred to nitrocellulose membranes. The immunoblots were probed with anti-MUC1-CD
 10 (Neomarkers, Fremont CA). Lysates not subjected to immunoprecipitation were similarly
 analyzed by immunoblotting with anti-MUC1-CD. Reactivity was detected with a
 horseradish peroxidase-conjugated second antibody and chemiluminescence. The results are
 shown in FIG. 1 and indicate that deletion of the four MUC1 carboxy-terminal amino acid
 residues abolishes the ability of MUC1 to colocalize with FGFR3.

- 15 **Example 2: Requirement for Carboxy-terminal Amino Acids for Co-localization of
 MUC1 with EGFR**

293 cells were transiently transfected with pRESpuo2-Flag-MUC1-CD(1-72) or
 pRESpuo2-Flag-MUC1-CD(1-68) that respectively expressed a MUC1 with a full length
 cytoplasmic domain:

20 CQCRRKNYGQLDIFPARDTYHPMSEYPTYHITHGRYVPPSSIDRSPYEKVSAG
 NGGSSLSYTNPAVAATSANL (SEQ ID NO: 131) or a truncated domain formed by
 deletion of the four carboxy-terminal amino acids:

CQCRRKNYGQLDIFPARDTYHPMSEYPTYHITHGRYVPPSSIDRSPYEKVSAG
 NGGSSLSYTNPAVAAT (SEQ ID NO: 132).

- 25 Cell lysates were prepared from subconfluent cells as described by Li et al. (1998).
 Equal amounts of cell lysate were incubated with anti-EGFR (Santa Cruz Biotechnology,
 Santa Cruz, CA) or mouse IgG. The immune complexes were prepared as described by Li et
 al. (1998), separated by SDS-PAGE and transferred to nitrocellulose membranes. The
 immunoblots were probed with anti-MUC1-CD (Neomarkers, Fremont CA). Lysates not
 30 subjected to immunoprecipitation were similarly analyzed by immunoblotting with anti-
 MUC1-CD. Reactivity was detected with a horseradish peroxidase-conjugated second
 antibody and chemiluminescence. The results are shown in FIG. 2 indicate that deletion of

the four MUC1 carboxy-terminal amino acid residues abolishes the ability of MUC1 to colocalize with EGFR.

Example 3: Interaction of MUC1 with PDZ Domains

The ability of the MUC1 cytoplasmic domain (CD) to interact with a panel of 28 human PDZ domain proteins was screened. A His-tagged MUC1/CD was produced to affect the screening. The CD of MUC1 was amplified by RT-PCR from cDNA derived from human breast cancer MCF7 cells. The MUC1/CD gene was cloned into a bacterial vector pEXP (Panomics Inc.) to generate a His-tagged fusion protein (pEXP/MUC1/CD). DH5 α E. Coli cells were transformed with pEXP/MUC1/CD and incubated overnight in 1 ml of LB medium containing 100 μ g/ml ampicillin (LB/AMP). Eighty μ l of the overnight culture was transferred to a tube of 4 ml of LB/AMP and allowed to grow until an OD₆₀₀ of approximately 0.5-0.8 was evident. IPTG was added to the culture at a final concentration of 0.5 mM to induce expression of the His-tagged MUC1/CD protein. After 4 hours, cells were harvested in 1X resuspension buffer (Panomics Inc.) and lysed by sonication. The lysate was centrifuged at 14000 rpm for 5 minutes at 4°C. The resulting supernatant (bacterial extract) was collected and stored at -80°C until use.

The TransSignal PDZ Domain Array kit (Panomics Inc.) was used comprising membranes on which the following 28 human PDZ proteins had been immobilized: MINT-2 d1, Mint-3 d1, Mint-3 d2, Mint-1 d1, Mint1 d2, CSKP, Dlg d1, Dlg1 d3, Dlg2 d2, Dlg4 d3, DVL1, DVL3, DVLL, GIPC, HtrA2, LIMK2, MPP2, NEB1, OMP25, hCLIM1, PTPH1, ZO-2 d1, hPTP1E d1, hPTP1E d5, RGS12, RIL, ZO-1 d3 and ZO-2 d3.

Membranes were submerged in a small tray with 20 ml of x1 blocking buffer (Panomics Inc.), and shaken at room temperature for 1 hour. The blocking buffer was removed and membranes rinsed twice with x1 Wash Buffer (Panomics inc.) at room temperature. The bacterial extract was diluted to a final concentration of 0.1 mg/ml in 20 ml Resuspension Buffer (Panomics Inc.). The membrane was incubated with the dilute bacterial extract overnight at 4°C with gentle shaking. After incubation, the membrane was washed three times with 40 ml 1X Wash Buffer at room temperature for 10 minutes each wash. The membrane was then incubated with 20 ml diluted Anti-Histidine HRP Conjugate (Panomics inc., 1:3000 dilution in 1X Wash Buffer) at room temperature for 1 hour. The membrane was then washed with 40 ml 1X Wash Buffer at room temperature for 10 minutes each wash. The membrane was then visualized using HYPERFILM ECL (Amersham Biosciences) utilizing the Detection Buffers as supplied by Panomics.

Binding was observed between his-tagged MUC1/CD and Mint-1 d2 (XII protein, PDZ domain #2), Mint-2 d1 (XIII protein, PDZ domain# 1), HtrA2 (high temperature requirement protein A2), PTPH1 (protein-tyrosine phosphatase H1), RIL (reversion-induced LIM protein) and OMP25 (mitochondrial outer membrane protein 25).

5 Example 4: Inhibition of MUC1 Cytoplasmic Domain Binding to PDZ Domains

His-tagged MUC1/CD (bacterial extract) was incubated in the absence or presence of a 20-fold molar excess of the 7-mer peptide AAASANL (SEQ ID NO: 133) with the appropriate membrane-immobilized PDZ domain, as described above in Example 4. The results are summarized in Table 2.

10

Table 2

Inhibition of Binding to MUC1/CD to Select PDZ Domains

PDZ	Protein conc. ng/spot	Relative Binding of MUC1/CD	
		no 7-mer peptide	Plus 7-mer peptide
Mint-3 d1	400	+++	-
Mint-3 d1	80	+	-
Mint-1 d2	400	++	-
Mint-1 d2	80	+	-
HTRA2	400	++	-
HTRA2	80	+	-
PTPH1	400	+	-
PTPH1	80	-	-
ZOP2	400	-	-
ZOP2	80	-	-

The 7-mer, AAASANL (SEQ ID NO: 133), inhibited the binding of his-tagged
 15 MUC1/CD to PDZ domains Mint-1 d2, Mint-2 d1, HtrA2 PTPH1, RIL. The PDZ domain ZOP2 was used as a negative control.

Example 5: Deletion of MUC1 PDZ Ligand Domain Abrogates MUC1-Dependent Resistance to Cisplatin

Human HCT116 colon carcinoma cells (ATCC, Manassas, VA) were cultured in Dulbecco's modified Eagle's medium/F12 with 10% heat-inactivated fetal bovine serum, 100 units/ml penicillin, 100 mg/ml streptomycin and 2 mM L-glutamine. HCT116 cells were transfected with pIRES-puro2, pIRESpuro2-MUC1 or pIRES-puro2-MUC1ΔSANL (MUC1 with the four carboxyl terminal amino acids SNAL deleted) as described (Li et al., 2001). Stable transfectants were selected in the presence of 0.4 mg/ml puromycin (Calbiochem-Novabiochem, San Diego, CA).

Cells were incubated with 100 μM cisplatin (CDDP; Sigma), for 24 and 48 hr. Visualization of viable cells indicated a substantially increase in the sensitivity to CDDP-induced cell death of HCT116 cells transfected with MUC1ΔSANL relative to cells transfected with full length MUC1. Data indicates that removal of the MUC1 carboxy-terminal PDZ ligand domain abrogates the ability of MUC1 to confer resistance to genotoxic agents.

Example 6: Preparation of Prokaryotic Expression Constructs Encoding PDZ Domains

PDZ domain containing genes or portions of PDZ domain containing genes were cloned into eukaryotic expression vectors in fusion with a glutathione S-transferase (GST) protein tags. Alternative tags include but are not limited to Enhanced Green Fluorescent Protein (EGFP), or Hemagglutinin (HA).

DNA fragments corresponding to PDZ domain containing genes were generated by RT-PCR from RNA from a library of individual cell line (CLONTECH Cat# K4000-1) derived RNA, using random (oligo-nucleotide) primers (Invitrogen Cat# 48190011). DNA fragments corresponding to PDZ domain-containing genes or portions of PDZ domain-containing genes were generated by standard PCR, using purified cDNA fragments (Table 3) and specific primers. Primers used were designed to create restriction nuclease recognition sites at the PCR fragment's ends, to allow cloning of those fragments into appropriate expression vectors. Subsequent to PCR, DNA samples were submitted to agarose gel electrophoresis. Bands corresponding to the expected size were excised. DNA was extracted by Sephaglas Band Prep Kit (Amersham Pharmacia Cat# 27-9285-01) and digested with appropriate restriction endonuclease. Digested DNA samples were purified once more by gel electrophoresis, according to the same protocol used above. Purified DNA

- fragments were coprecipitated and ligated with the appropriate linearized vector. After transformation into *E. coli*, bacterial colonies were screened by colony PCR and restriction digest for the presence and correct orientation of insert. Positive clones were inoculated in liquid culture for large scale DNA purification. The insert and flanking vector sites from the purified plasmid DNA were sequenced to ensure correct sequence of fragments and junctions between the vectors and fusion proteins.

Table 3
PDZ Domains Used in Screening Assays

Gene Name	GI or Acc#	PDZ#	Sequence fused to GST Construct
26s subunit p27	9184389	1	RDMAAHKEAMSRLIQSESGQFPRAFAKVNISISFGSPSTAGLQ VDDEIVFSGSVNTQNTQSLNIGSVVQHSSEGAIAPIITLLSVSM
AP6	430993	1	LRKEPIIITVTLKQNGMGLSIVAAGAGQDKLGLYKSVVZKGG AADVDGRLLAAGDQLLSVDGRSLVGLSQERAAIIMLTITSSVVT EVAKQG
AIPC	12751451	1	LIRPSVISIIGLYKEKKGGLGFSIAGGRDCIRGQMGIHVKTIFPNGS AAEDGRLEKGEDEILDVNGIPIKGLTFQEAHTFKQIRSGFLVLTVR TKLVSPSITNSS
AIPC	12751451	2	GISSLGRKTPGPKDRIVMEVTTNKPEPRVGLGIGACCLALENSPFG IYHSLAPGSAVKMESNLIRGQDQILEVNSVNVRAHAAISKVHAITS KCPGPGVRLVIGRHPNPKVSEQEMDEVIARSTYQESKIANSS
AIPC	12751451	3	QSENEEDVCFIVLNRKEGSGLGFSVAGGTDEVEPKSITVHRVFSQ GAASQEGTIMNRGDFLLSVNGASLAGLAHGNVLKVLHQAQLHK DALVVIKKGMDQPRPSNSS
AIPC	12751451	4	LGRSVAVHDALCVELKTSAGLGLSLDGGKSSVTGDGPLVIKR VYKGAEEAQGHEAGDEILANGKPLVGLMHFDawnNMKSVP GPVQLIRKHNSS
alpha actinin-2 associated LIM protein	2773059	1	REBGGMPQTIVLPAAWGFRLSGGIDFNQPLVITRTTPGSKAAA ANLCPGDVLAIDGFGFTESMTHADGGDRKIAAAHQLCLKIDRGE THLWSPHSIV
APXL-1	13651263	1	ILVEVQLSGGAPWGFITLKGREHGEPLVITKIEEGSKAAAVDKL LAGDEIVGINDIGLSGFRQEAICLVKSGHITKLVLVKNSS
Atrophin-1 Interacting Protein	2947231	1	REKPLFTDRASQLKGTFTSTLLKSSNMGPFGIITGGDEPDEFQV KSVIPDGPAADGKMETGDVIVYNEVCVLGHTHADVVKLFQS VPIGQSYNLVLCRGYP
Atrophin-1 Interacting Protein	2947231	2	LSGATQAELMLITIVKGAQGGFTIADSPTQQRVKQLDIQCGFG LCEGDILVEINQQNVQLSHTEVVDLKDCPIGSETSLIHRGGFF
Atrophin-1 Interacting Protein	2947231	3	HYKELDVHLRRMESGFGFRITGGDEFGQPIILGAVIAMGSARD GRHPGDELVVYDGIPIVAGKTHRYVIDLMHHAARNGQVNLTV RRKVLGG
Atrophin-1 Interacting Protein	2947231	4	EGRGISSEHSLQTSDAVIRKENBGFVVISSLNRPESGSTITVPHK IGRIDGSPADRCALKVGDRLAVNGQSINMPHADIVKLKDA GLSVITRIIPQEL
Atrophin-1 Interacting Protein	2947231	5	LSDYRQPDQDFVFTVDMKGAEGFGFSIRGGREYKMDLYVRL AEDGPAIRNGRMVRVGDQIEINGESTRDMTHARAIELIKSGRRV RLLLKRGITGQ

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Atrophin-1 Interacting Protein	2947231	6	HESVIGRNPEGQLGFELKGAENGQFPYLGEVKGPKVAYESGS KLVSBEILLEVENETPVAGLTIRDVLAVIKHCKDPLRLCKVKGQGG IHR
CARD11	12382772	1	SVGHVRGPGSPVQHITLNGDSLTSQTLILLGNGARSPFVSVKP GSLARKAGLRREGHQLLLLEGICIRGERQSVPLDTCCKEAEHWITQ RCSGPVTLHYKVNHBGYRK
CARD14	13129123	1	RRPARRILSQVTMLAFQGDALLEQISVIGGNLTGFIHRVTFPGSA ADQMALRFGTQIVMVDYASEPLFAVLEDDTLEAVGLLRV DGFCCLSVKVNTDGYKR (SEQ ID NO:115)
CASK	3087815	1	TRVRLVQFQKNTDEPMGHTLKMNELNHCIVARIMHGGMIHRQG ITLVGDEIREINGISVANQTVEQLQKMLREMRGSIPTKIVPSYRT QS
Connector Enhancer	3930780	1	LEQKAVLEQVQLDSPGLEIHTTSCNQHFVSVQVDTPQVTDLSRLQ IQPGDEVVQINEQVVVGWPRKNMVRILLREPAGLSLVLKCKIP
Cytohesin Binding Protein	3192908	1	QRKLVTVEKQDNETHFGFEGSYRPNQNAACSSHMFTLCKIQEDS PAHCAGLQAGDVLANINGVSTEGFTYKQVVDLIRSSGNLLTIET LNG
Densin 180	16755892	1	RCLIQTKGQRSMDGYPEQFCVRIEKNPGLGFSISGGISGQGNPFK PSDKGIFVTRVQPDGPASNLLQPGDKILQANGHSFVIMHEKA VLLKSFQNTVDLVQRELT
DLG1	475816	1	IQVNGTDADYEYEITLERGNSGLGFSIAGGTDNPHIGDDSSIFT KHTGGAAAQDGRLRVNDCLQVNEVDVRDVTHSKAVEALKRA GSIVRLVYKRRN
DLG1	475816	2	IQLIKGPGLGFSIAGGVGNQHPGDNSIYVTKIEGGAAHKGDK LQIGDKLLAVNNVCLVEEVTHEEAVTALKNTSDFVYLVAKPIS MYMNDGN
DLG1	475816	3	ILHRGSTGLGFNTVGGEDGEGIFISFILAGPADLSGLRKGDRIS VNSVDLRAASHEQAAAAALKNAQOAVTVAQYRPEYSR
DLG2	12736552	1	ISYVNGTEIEYFEETLERGNSGLGFSIAGGTDNPHIGDDPGIFT KIIPGAAAEGRRLRVNDCLRVNEVDVSEVSHSKAVEALKBAG SIVRLYVRRR
DLG2	12736552	2	IPILETVVEIKLFKGPGLGFSIAGGVGNQHPGDNSIYVTKIIDGG AAQKDGRLQVGDRLLMVNNYSLEEVTHEREAVALKNTSEVYVL KVGKPTITVMTDPIYPPNNS
DLG2	12736552	3	ILBEGPRKVLHKGSTGLGFNTVGGEDGEGIFISFILAGPADLS GELQRGDQILSVNGDILRGASHEQAAAAALKGAGQVTTHAQHP EDYARFEAKIHDLNSS
DLG5	3650451	1	GIPYVEEPRHVKVQKSGSEPLGISIVSGEKGHHYVSKVTVGSIAHQ AGLEYGDQLEENGINLRSATEQQARLIIGQQCDTITLAQYNPH VHQLRNSSZLTD
DLG5	3650451	2	GILAGDANKTKLEPRVVEFKKSQLELGVHLGGNHLGVFAEV EDDSPAKGPDGLVPDGLILEYGSLDVRNKTVEEYVEMLKPRD GVRLKVQYRPEEHVTD
DLG6, splice variant 1	14647140	1	FTSPEIQELRQMLQAPHFKALLSAHDTIAQKDFEPLLPPLPDNIFE SBEAMRIVCLVKNQQLGATIKRHEMTGDILVARIHGGLAERS QLLYAGDKLVEVNGVSGELDPEQVIHILAMSRGTIMFKVVPVS DPPVNSS
DLG6, splice variant 2	AB053303	1	FTSPEIQELRQMLQAPHFKGATIKRHEMTGDILVARIHGGLAER SGLLYAGDKLVEVNGVSGELDPEQVIHILAMSRGTIMFKVVPV SDPPVNSS
DVL1	2291005	1	LNIVTVTLNMRHHFLGSIVGQSNDRGDGGHYIGSIMKGGAVA ADGRIEFGDMLLQVNDVNTNMSNDDAVRVLRREIVSQTGPISLT

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			VAKCW
DVL2	2291007	1	LNITVTINMEKYNFLGISIVGQSNERGDGGIYGISMKGGA VAA DGRIEPGDMLLQVNDMNFENMSNDDAVRVLRDIVEKPGPILVT VAKCWDSPSPQNS
DVL3	6806886	1	ITVTINMEKYNFLGISIVGQSNERGDGGIYGISMKGGA VAAADG RIEPPDMLLQVNEINFENMSNDDAVRVLREIVHKPGPITLTVAK CWDSPSP
ELFIN 1	2957144	1	LTTQQIDLQGPWPWFRLVGRKDFEQPLAISRVTPGSKAALANL CIGDVITADGENTSNMTHLEAQNRIKGCIDNLTITVAREHKV WSPLVTNSS
ENIGMA	561636	1	IFMDSFKVVLEGPAPWGRFLOQGGKDFNVPLSISRLTPGGKAAQA GVAVGDVWVLSIDGENAGSLTHIEAQNKIRACGERLSLGSRAQF V
ERBIN	8923908	1	QGHLELAKQIRVRVEKDPELGFSGGSGVGRGNPFPPDDDGIFV IRVQPEGPASKLLQPGDKHQANGYSFNIHGGQAVSLTKTFQNT VELIIVREVSS
EZRIN Binding Protein 50	3220018	1	QMSADAAGAPLPRLLCCLEKGPNGYGFHLHGEKKGKLGQYRIV EPGSPAEEKAGLLAGDRLVVEVNGENVEKETHQVQVVSRIARAALNA VRLLVDPEDTDLQKLGVQVREELLRAQEPGAQEPFAAAEV QAGNENENEPRIADKSHPBQRELRNSS
EZRIN Binding Protein 50	3220018	2	IQQRELRLPRLCTMKKGPSGYGFNLHSDKSKPGQFIRSVDPDSPA EASGLRAQDRIVEVNGVCMGKQHGVDVVSARAGGDETKLLV VDRETDDEFKNS
FLJ00011	10440352	1	KNPSGELKTVTLKMKQSLGISISGGIESKVVQPMVKIEKIFPGA AFLSGALQAGFELVAVDGENLEQVTHQRAVDITIRAYRNKARE PMELVVRVPGSPRPSFSD
FLJ11215	11436365	1	EGHSHPRVVELPKTEEGLGFMGGKEQNSPTYIRIIPGGIADRH GGLKRGDQLLSVNGVSVEGHEHEKAVELLKAAQGVKLVVRY TPKVLHEME
FLJ12428	BC01204 0	1	PGAPYARKTFTIVGDAVGVGFVVRGSKPCHQAVDPSPGAAAA GMKVCQFVSVNGLNLVHDYRTVSNLITGPRTIVMEVMBEL EC
FLJ12615	10434209	1	QGYGGETVKIVRIEKARDIPLGATVRNEMDSVIIRIVKGGAAEK SGLLHBGDEVLEINGIEIRGKDVNRVFDLLSDMHGILTFVLIPSQ QIKPPPA
FLJ20075	7019938	1	ILAHVKGHEKEVNRYKSEDSGLTITDNGVGVAHKKRIKDDGVID SVKTCVGDHIESINGENIVGWRHYDVAKKLKLKKBTLITMKL IHPKKAPEI
FLJ21687	10437836	1	KPSQASGHFSVELVRGVAGFGLTLGGGRDVAGDITPLAVRGLLK DGPAQRGCRLEVGDLVHNGESTQGLTHAQAVERTRAGGPQL HLVIRRPLETHPGKPRGV
FLJ31349	AK05591 1	1	PVMSQCACLEEVLHLPNIKPGEGGLMYIKSTYDGLHVITGTTNS PADRSQKIHAGDEVQVQNTVVGWQLKLNVLKLRNPTGVV LLKKRPTGSFNTPEFIVTD
FLJ32798	AK05736 0	1	LDEDEDSVKIRLVKNREPLGATIKKDEQTAIVARIMRGGAAD RSLIITVGDLEREVNGPVEDKRPETIQLAQSQGAITFKIIPGSK EETPSNSS
GoRASPI	NM03189 9	1	MGLGVSAEQPAGGABGFHLHGVOENSPAQQAGLEPYDFDITIG HSRLNKENDITLKALLKANVKEPKLEVPNMKTMVRREVVEVP SNMWGGQGLLGASVRFCSFRASE

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GoRASP1	NM031892	9	RASBQVWHVLDVEPSSPAALAGLRPYTDYVVGSDQILQESDDF TLISHHGKPLKLMVYNSKSDSCREVTVTPNAWGGEGSLGCGI GYGYLERIPTQ
GoRASP2	13994253	1	MGSSQSVIEPGGGTEGYHVLRVQENSPGHRAGLEPPFDFVISING SRLNKDNDTLKDLLKANVBPVKMLLYSSKTLLERTSVTPSNL WGGQQLLGVSIRCFDGDANE
GoRASP2	13994253	2	NENVWHVLEVENSPAALAGLRPHSDYIIGADTMNESEDLSL IETHAKPLKLYVNTDNTDNCREVIITPNSAWGGEGSLGCGIGY GYLERIPTQ
GRIP 1	4539083	1	VVELMKKEGTTGLTVSGGIDKDGKPRVSNLRQGGIAARSQDL DVGDYKAVNGINLAKFRHDEIISLKNVGERVVLEVEYE
GRIP 1	4539083	2	RSSVITRTVEVTLHKEGNTFGFVIRGGAHDRNKRSPVVIICVRP GGPADREGTIKPGDRLLSVDGIRLLGTHAEAMSILKQCGQEAAL LLIEYDVSVMDSVATASGNSS (
GRIP 1	4539083	3	HVATASGPLLVEVAKTPGASLGVALTSMCCNKQVIVIDIKKSA SIADRCGALHVGDDHLSIDGTSMEYCTLAERATQFLANTDQVKL EILPHHQTRIALKGPNSS
GRIP 1	4539083	4	HVATASGPLLVEVAKTPGASLGVALTSMCCNKQVIVIDIKKSA SIADRCGALHVGDDHLSIDGTSMEYCTLAERATQFLANTDQVKL EILPHHQTRIALKGPNSS
GRIP 1	4539083	5	ABSVIPSSGTFHVKLPKKHNVBLGITSSPSSRKPGDPLVISDIKKG SVAHRTGTILEGDKLLAIDNIRLDNCSMEDAVQILQCCEDLVKL KIRKDEIDNSD
GRIP 1	4539083	6	IYTVELKRYGGFLGITSGTEEPFDPHSSILTKGGLAERTGAIHGD RILAINSSSLKKGKPLSEAIHLQMAGETVTILKIKKQTDQASA
GRIP 1	4539083	7	IMSPTPVELHKVTLKDSMDDEFGFSVADGILEKGVYVKNIRP AGPGDLGGGLKPYDRLLQVNHVKTRDPDCLLVVPLAESGNKLD LVISRNPLA
GTPase Activating Enzyme	2389008	1	LSRGCEIRELALPRDGGQRLGFEVDAEGFVTHVERFTIABTAGL RPGARLLRVCGQTLPSLRPEAAQLLRSAPKVCVTVLPFDESGR FRNSS
Guanine Exchange Factor	6650765	1	CSVMIFEVVEQAGAILLEDGQELDSWYVILNGTVIHSHPDGKVEN LFMGNISFGHTPTLDEQYMHGIVRTKVDCCQFVCIQAQDYWRIL NIIVKNTHKVEEBSGIVMVHEFTVD
HEMBA 1000505	10436367	1	LENVIAKSLIKSNESGYGLEDKNCVPIIKLVEKGSNAEMAG MEVGGKIFAIINGDLVFMPPNEVDCLFKSCLNSRKLPLVLVSTK P
HEMBA 1000505	10436367	2	PRFTVKIPDSADGLGQIRGFGPGSVVHAVRGRTVAAAAGLHPG QCHKVGNGINYSKETHASVIAHVTA CRKYRRPIKQSIONSS
HEMBA 1003117	7022001	1	EDFCYVFTVELERGPSGLGMGLIDGMHTHLOAPLYTIQTLLPS PAAADGRLSLGRILEVNGSSLLGLGYLRAVDLRHGGKKMRFL VAKSDVETAKKI
HSPC227	7106843	1	NNELTQFLPRTITLTKPPGAQLGNIRNGGKASQLGIFISKVIPSD ABRAGLQBGDQVLAVNDVDFQDIEHSAVELIKTAREISMVR EPPYNYHRQKE
HTRA3	AY04009	1	LTEFQDKQIKDWKKRFIGRMRTITPSLVDELKASNPDFEVS YVQEVAPNPSQRRGGHQDGDIVKVGNGRPLVDSSELQBAVLTESP LLEVRNGNDLLPSNSS (SEQ ID NO:158)
HTRA4	AL57644	1	HKKYLGLQMLSLTVPLSEELKMHYPDFPDVSSGVYVCKVVEGT AAQSSGLRDHEDVIVNINGKPIITTTDVVKALDSDSLMAVLRLK DNLILLTVNSS

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INADL	2370148	1	ITWQIEYIDIERPSTGGGLGFSVVALRSQNLGKVDIFVKDVQPGSVA DRDQRLKENDQLAINHTPLDQNIHQQAIALLOQTITGSLRLIVA RPFVHTKSSSTSSB
INADL	2370148	2	LPETVCWGHVEEVELINDGSLGFGIVGGKTSVGVVKTIVPGGL ADRDGRLQTGDHILKGGTNVQGMTSEBQVAQVLRNCGNSVRM LYARDEPAGDISVTNSS
INADL	2370148	3	PGSDSLFETYNVELVRKDGQSLGIRIVGYVGTSHETGEASGIYVK SIIPGSAAYINGHIQVNDKIVAVDGVNIQGFANHDVVEVLNAG QVVHILVVRKTSSTSRHHD
INADL	2370148	4	NSDDAELQKYSKLLPIHTLRLGVEVDSFDGHHYISSIVSGGPVDT LGLLQPEDELLEVNGMQLYGKSRREAVSFLEKVEVPPFTLVCCRR LFDDEAS
INADL	2370148	5	LSSPEVKIVELVKDCKGLGFSILDYQDPLDPTRSVIVRSVLADG VAERSGGLLPGRDLVSVNEYCLDNTSLAEAVHILKAVPPGLVHL GICKPLVHITVTD
INADL	2370148	6	PNFSHWGPFPRIVEIFREPNSVLGISIVVQGTIVIKRLKNGEELKGM KQVLEDSFAGKTNALKTGDKILEVSGVDLQNASHEAVEAIAKN AGNPVVFVQSLSSTPRVFNHNKANSS
INADL	2370148	7	FGELHIELEKDNGLGLSLAGNKDRSRMSIFVVGINPBGAAAD GRMRIGDELLENNQILYGRSHQNASAIKTAPSKVKLVFIRNED AVNQMANSS
INADL	2370148	8	PATCPVPGQEMIEISKGRSGLGLSIVGGKDTPLNAIVIEVEYEE GAAADGRLWAGDQILEVNGVDLRNSSHEAITALRQTPQKVR LVVY
KIAA0147	1469875	1	ILTLTLRQTGGGLGISIAGGKGSTPYKGDDEGIFISRVSEEGFAAR AGVRVGDKLLEVNGVALQGAHHEAVEALRGAGTAVQMRVW RERMVEPENAEFIVTD
KIAA0147	1469875	2	PLRQRHVACLARESRGLGFSIAGGKGSTPYRAGDAGIFVSRIAE GGAAHRAAGTLQVGDRLVSLNGVDVTEARHDHAVSLTAASTPI ALLEREAGG
KIAA0147	1469875	3	ILEGPPYVEEIRLPRAGGPLGLSIVGGSDHSSHPFGVQEPGFISK VLPRGLAARSGLRVGDRILAVNGQDVRDAITHQEAVSALLRPCI ELSLVRRDPAEFIVTD
KIAA0147	1469875	4	RELCTQKAPGERLGISIRGGARGHAGNPRDPTDEGIFISKVSPGTA AGRDGRLRVGLRLLEVNGQSLGLTHGEAVQLRSVGDTLTLVL VCDGFESTDAALEVS
KIAA0303	2224546	1	PHQPIVHSSGKNYGFITRAIRVYVGDSDIYTVHHVWNVEEGSP ACQAGLKAGDLITHINGEPVHGLVHTEVIELLLKSNKNSITITP F
KIAA0313	7657260	1	HLRLNIACAANKRRRLMTLTKPSREAPLPHILLOGSEKGFQFV DSVDSGSKATEAGLKRGDQILEVNGQNFENQLSKAMILRNNT HLSTIVKTNLVPFKEILLTRISEEKRNAPNSS
KIAA0316	6683123	1	IPPAPRKVEMRRDPVLGFGFVAGSEKPVVVRSVTPGGPSEGLIP GDQIVMINDEPVSAAPRERVIDLVRSCKEISILLTVIQPYTSPKSEFI VID
KIAA0340	2224620	1	LNKRTITMPKDSGALLGLEKVVGKMTDLGRIGAFTIKVKKQSL ADVVGHLRAGDEVLEWNGKPLPGATINEBVNILESKSEFPQVEH VSRPFGIDPRIHRD
KIAA0380	2224700	1	QRCVHIQKDQHGFGFTVSGDRIVLVQSVRPGGAAMKAGVKBGD RIIKVNGMTVNTSSHEVVKLIKSGAYVALTLGSS
KIAA0382	7662087	1	ILVQRCVHIQKDDNGFLTVSGDNPVVFQSVKEDGAAMRAGVQ TGDRIKVNGTLVTHSNHLEVVKLIKSGSYVALTVQGRPPGNSS

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KIAA0440	2662160	1	SVEMTLRRNLGQLGFHVNYEGIVADVEPYGYAWOAGLRQGS RLVEICKVAVATLSHEQMIDLLRTSVTVKVVIPPHD
KIAA0545	14762850	1	LKVMITSGWEIVDMTLRRNLGQLGFHVKYDGTVAEVEDYGF AWOAGLRQGSRLVEICKVAVVTLTHDQMIDLLRTSVTVKVVIP PFEDGTTPRGW (SEQ ID NO:179)
KIAA0559	3043641	1	HYIFPHARIKTRDSKDHVTSNGNLGRIVVGKKEPGHSGEIGAYT AKILPGGSABQTGLMEGMQVLEWNGIPLTSKTYEEVQSIIISQQ SGHAICVRLDINML
KIAA0561	3043645	1	LCGSLRPPIVIBSSGKKYGFSLRAIRVYMGDSVYTVHHVWVSV EDGSPAQEAAGLRAGDLITHINGESVLGLVHMDVVELLKSNGKI SLRTTALENTSIKVGNS
KIAA0613	3327039	1	SYSVTLTGPGPWGFRLLQGGKDFNMPLTISRITPGSKAAQSQLSQ GDI.VVAIDGVNTIDMTLHLEAQNKKISASYNLISLTQKSKNS
KIAA0751 RIM2	12734165	1	ILNEEHSHSDKHPTVWQPSKDGRLIGRLINLKRKIDGVSVPDS GAMLGLKVVGGKMTESGRLCAFTIKVKKGSLADTVGHLRPGD EVLEWNGRLQGGATFEVYVNILESKEPEQVLEVVSRPIG
KIAA0807	3882334	1	ISALGSMRPFMIHRAGKKYGFILRAIRVYMGDSVYTVHHMVWV HVEDGGPASAAGLRQGDILTHVNGEPVHGLVHTEVVELILKSON KVAISTPLENS
KIAA0858	4240204	1	FSDMRISINQTPGKSLDFGFTIKWDIPGIFVASVEAGSPAESQLQ VDDEIADNNTKFSYNDKSKEWEEAMAKAQETHGLVMDVRRYVGK AGSPE
KIAA0902	4240292	1	QSAHLEVIQIANIKPSEGLGMYIKSTYDGLHVITGTTENSPADRC KKHAGDEVIQVNEQIVVGWQLKNLVNAIREDPSGVILTLLKKR PQSMILTASA
KIAA0967	4589577	1	ILTQTLLPVRHTVKIDKDITLLQDYGFBISESPLTVVAVTAGGSA HGKLPFGDQILQMNNEPAEDLSWERAVIDLREAEADSLITVVR TSGVPKSSNS
KIAA0973	4589589	1	GLRSPITIQSGKKYGFILRAIRVYMGDITVYVHHIVWHVEEG GPAQEAAGLCAGDLITHVNGEPVHGMVHPEVVELILKSGNKVAV TTTFF
KIAA1095	5889526	1	QGEETKSLTLVLRHDSGSLGFNIGGRPSVDNHDGSSSEGFVSKI VDSGPAAKEGGLQIHDRHEVNGRDLSRATHDQAVEAFKTAKEP IVVQVLRRTPTKMTF
KIAA1095	5889526	2	QEMDRERLEEEVDLYRMNSQDKLGLTVCYRTDDEDDIGIYISE IDPNSIAAKDGRIREGDRIQINIEVQNRREAVALLTSEENKNFS LLIARPELQD
KIAA1202	6330421	1	RSFQYVPVQLQGGAPWGFTLKGGLHECEPLTVSKIEDGGKAAAL SQKMTGDELVNINGTPLYGSRQEAALLIKGSFRILKIVRRRNA PVS
KIAA1222	6330610	1	ILEKLELFPVELEKDEDLGSIIGMGVADAGLEKLGIFVKTVT EGGAAQRDGRQVNDQVEVDGSLVGVTONFAATVLRNTKGN VRFVIGREKPGQVS
KIAA1284	6331369	1	KDVNVYVVPKRLTVIKAKBQLKLEVLVGHBTQKWSWRTGK QGDGERLVVHGLPGGSAMKSGQVLIGDVLVAVNDVDVTITEN ERVLSICPGPMQVKLTENAYDVKRET
KIAA1389	7243158	1	TRGCBTYEMTLRRNLGQLGFHVNFEGIVADVEPFGFAWKAGL RQGSRLVEICKVAVATLTHEQMIDLLRTSVTVKVVIPPHDGGSP RR
KIAA1415	7243210	1	VENILAKRLILPOEEDYGFDEEKNKAVVVKSVQRGSLAEVAG LQVGRKIYSINEDLVFLRPFSEVESILNQSFCSRPLRLVATKAK BIKIP (SEQ ID NO:195)

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KIAA1526	5817166	1	PDSAGFGVRLVSLRRAKAHEGLGFSIRGGSEHGVGIIYVSLVEP GSLAHKFGRLRGDQLRVNDEKSLARVTHAEAVKALKGSKKLVL SVYSAGRPGGYYVTHIEFIVTD
KIAA1526	5817166	2	LQGGDEKKVNLVLGDGRSLGLTRGGAEYGLGIYITGVDPGSEA EGSGKLVGDQILEVNWRSFLNLHDEAVRLKSSRLHLITVKDV GRLPARTITVDEFTVTD
KIAA1526	5817166	3	WTSGAHVHSGPCBEKCGHFGHROPLPRIVTIQRGGSAHNCGQL KVGHVILEVNLTLRKEHREAAARIAEAPKTKDRDYDFLDSL
KIAA1620	10047316	1	ELRRAELVEIIVETEAQTGVSGINAVAGGKEGIFVRELREDSAA RSLSLQEGDQLLSARVFFENFKYEDALRLQCAEPYKVSFCLKR TVPTGDALRLP
KIAA1634	10047344	1	PSQLKGVILVRASLKKSTMGFGFTIGGDRPDEFQVKNVLKDGPF AAQDGKIAPGDVIVDINGNCVLGHITADVVQMFLQVPVNGYV NLTLCRGYPLPDDSED
KIAA1634	10047344	2	ASSGSSQPELVITPLIKGPGFGFALADSPGTQGVKMLDSQWCQ GLQKDGDIKEIYHQNQVNLTHLQVVEVLKQFVVGADVPLILRG GPPSPITKAKM
KIAA1634	10047344	3	LYEDKPPILTNTFLSNPRTTADPRILYEDKPPNITKDLVFLRKQF SGGFRVLGGDQPDQSYTGAIPLGAAEKDGRLAARDELMCIDG TPVKGSKHQVLDMITTAARNHGVLLTVRRKIFYGKQPEDDS GSPGHIHRLT
KIAA1634	10047344	4	PAPQFPYDVVLQKRENEGFGFVILTSKNKPPPGVIPHIGRIVIEG SPADRCGLKLVGDHSAVNGQSIVELSHDNIVQLIKDAGVTVTL TVIAEEHHHGGPS
KIAA1634	10047344	5	QNLGCPYVELERGPGRGFGFSLRGKKEVNMGLFLRLAEDGPAIK DGRHIVGDQIVEINGEPTQGIITHIRAIELIQAGGNKVLILLRPGT GLIPDHGLA
KIAA1719	1267982	0	TVVVELIKKEGSTLGLTISGGTDKDGKPRVSNLRPGGLAARSDDL NIGDYIRSVNGIHLTRLRHEDEITLLKNVGERVVLEVEY
KIAA1719	1267982	1	ILDVSLYKEGNSFGFVLRGGAHEDGHKSRLVLTIVYRFGGPAD REGSLKVGDRLLSVDGIPLEGASHATALATLRQCSHEALFQVEY DVATP
KIAA1719	1267982	2	IHTVANASGLPMVEIVKTPGSALGSLITTSILKNKSVITIDRIKPA VVDKSGALHPGDHILSDIGTSMHECSLLEATKLASISEKVRLEIL FVPSQORPL
KIAA1719	1267982	3	IQIVHTTETEVVLGCDPLSGFGLQGGGIFATETISSPPLVCFIEPD SPAARRCGLLQVGDRLVINGIATEDGTMEENQLLRDAALAHK VVLEVEEDVAESV
KIAA1719	1267982	4	IQFDVAESVTPSSGITHVKLPKKRSVELGHTISSASRKRGEPLISDI KKGSVAHRTGTLEPGDKLLAIDNIRLDNCPMBDAVQLRQCEDL VKLKIRKDEDN
KIAA1719	1267982	5	IQTGAVSYTVELKRYGGFLGHTISGTEBFPDPVVISGLTKRGLAE RTGAHVGDRLAINNVSLKGRPLSEAHILLQVAGETVTLKIKKQ LDR)
KIAA1719	1267982	6	LEMEHILLPTPLEMHKVTILHKDFMRHDFGFSVSDGLEKGVY VHTVTPDGAHRGGLQPDVRLQVNHVTRTRDFDCCCLAVPLLA AGDVLEILISKKPIHARS
LIM Mystique	12734250	1	MALTVDVVAGPAPWGFRITGGGRDFHTPMVTKVAERGAKAD LRPGDIIIVAINGESAEGLMLHAEAQSKIRQSPSPRLQLDRSQATS FGQT
LIM Protein	3108092	1	SNYSVSLVGPAPWGFRLLQGGKDFNMPLTISLKDGGKAAQANY RIGDVLVLSIDGNAQGMTHLEAQNKIKGCTGSLNMTLQAS

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LIMK1	4587498	1	TLVEHSKLYCGHCYVQTVVPIVHQLFDSFGSHLPHTVTLVSP ASSHGKRGSLVSIDPHGPGCGTEHSHTVRVQGVDFGCMSPDV KNSIHVGDRLILEINGTPRNVPLDEIDLIIQETSRLQLTLEHD
LIMK2	1805593	1	PYSVTLISMPTATEGRRGFSVSVESACSNEYATTVQVKEVNRMH SPNNRNAIHPGDRILEINGTPVTRLVBEVEDAISQTSQTLLIE HD
LIM-RIL	1085021	1	IHSVTLRGPSFWGFRVLVGRDFSAPLTISR VHAGSKASLAALCPGD LIQAINGESTELMTHLBAQNRIKGCCHILTLVSRSPE
LU-1	U52111	1	VCYRTDDEEDLGIVVGBVNPNSIAAKDGRREGDRIQINGVDVQ NREGAVAILSQEENTNISLLVARPESQLA
MAGI1	3370997	1	PSELKGGFIHTKLRSSRGFGFTVVGDEPDKFIQKSLVLDGPA ALDQKMETGDIVVSNDTCVLGHTHAQVVKFIQSPIGASVDLE LCRGYPLFPDGDHHRD
MAGI1	3370997	2	PATQPELTVHIVKGPMGFGFTIADSPGGGGQVRVKQVDSPRCRG LKEGDLIVEVKNKNVQALTHNQVVDMLVECPKGS EVTLLVQRGGNSZ
MAGI1	3370997	3	QATQEQDFYTVLELGAQGFGLSRGGREYNMDLYVLRLAED GPAERCGKMRIGDEILEINGETTKNMKHSRAELKNGGRRVRLE LKRG
MAGI1	3370997	4	PGVVSTVQPYDVEIRRGEGFGFVIVSVSRPEAGTITFAGNA CVAMPHKIGRIEJGSPADRCGLKVQDRILAVNGCSITNKSHSDI VNLKEAGNTVTLRIIPGDESSNAEFTVD
MAGI1	3370997	5	PDYQEQDIFLWRKBTGFGFRILGGENPGEPTIYGHVPLGAADTD GRLRSGDELICVDGTPVIGKSHQLVVQLMQAAKQGHVNLTVR RKVVFAVPKTESS
MGC5395	BC012477	1	PAKMKRBETTRELLPNWQSGSGHGLTIAQRDDGVFVQEVNTQN SPAARTGVVKEGDQVIGATITFDNLQSGHEVTQLNLTMGHRTVG LKLHRKGDRSPNS
MINT1	2625024	1	SENCKJVFIEKQKGEILGVVIVESGWSILPTVIANMMHGGPAE KSGKLNIGDQIMSINGTSLVGLPLSTQCSIKKQNSRVKLNIVR CPPVNS
MINT1	2625024	2	LRCPPVTTVLRFPDLRYQLGFSVQNGIICSLMRGGIAERGGVRV GHRIBINGQSVVATPHEKIVHLSNAVGPHIMKIMPAAMYRL NSS
MINT3	3169808	1	HNGDLDFHSNSDNCREVHLEKRRGEGLGVALVESGWSILPTA VIANLLHGGPAERSGALSIGDRLTAINGTSLVGLPLAACQAAVR ETKSQTSVTLISVHCPPVT
MINT3	3169808	2	PVTIAHHRPHARBLQGFCEVDGHCISLLRGGIAERGGIRVGHRIE INGQSVVATPHARHRLTEAYGEVHKTMPAATYRLLTG NSS
MPP1	189785	1	RKVRILQFEKVTEBPMGITLKLNEKQSCVTARILHGGMIHRQGS LHVGDLEINGTNTVNHSDVQLQKAMKEKGMISLKVFNQ
MPP2	939884	1	PVPPDAVRMVGIRKTAGEHLGVTFVEGGELVIARILHGGMVA QQGLLHVGDLEKVNQFVGSDFRALQELLRNASGSVILKILPNY Q
MPP3	1022812	1	NIDEHDFDEBSVKIVRLVKNEKPLGATIRRDHISGAVVVARIMRG GAADRSGLVHVGDELEVNGLAVLEKRPDEISQLAQSGSITLK IIPATQBEDR
MUPP1	2104784	1	QGRHVEVFELLKPPSGGLGFSVVGRLSENHGLGIFVQIBQEGSV AHRDGRLEKETDQLAINGQALDQTTHHQASILQKAKIDTVQLVI ARGSLPOLV
MUPP1	2104784	2	PVHWOHMETHELVDNDSGLGFGIIGKATGVIVKTLPGVADQ HGRLCSGDHILKIGDIDLAMSSBQVAQVLRQCGNRVKLMAR

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			GAHERTAPT
MUPP1	2104784	3	QSEETDVEITKNVQGLGTTIAGYIGDKKLFSGIFVKSITKSSAV EHDGRIGIQDQIIAVDGTNLQGFNTQQAQVEVLRETTGQTVLLTLM RRGMKQBA
MUPP1	2104784	4	LNVEIVVAHVSKFSNSGLGISLEATVGHIFIRSLVPEGPVGHSG KLFSGDEILEVNGITLLGENHQDVVNLKBLPIEVTMYVCCRRTVP PT
MUPP1	2104784	5	WEAGIQHIELEKSGKGLGFSILDYQDFIDPASTVIHRSVPGGHAE KDGRLLPGDRLMFVNDVNLNSSLEEAVEALKGAPSGTVRIGV AKPLPLSPENSS
MUPP1	2104784	6	RNVSKESFERTINIAKONSSLGMTVTSANKDGLGMIVRSIHGGAI SRDGRIGAIGDCLISINEESTISVTNAQARAMLRHSLGPDIKITYV PAEHLLE
MUPP1	2104784	7	LNWNQPRRVELWREPSKSLGISVGGRGMSRLSNGEVMRGIFI KHVLEDSFAGKNGITLCPGDRIVEVDGMDLRDASHEQAVEAIRK AGNVVFMVQSTINRPRKSLPLSL
MUPP1	2104784	8	LTGELHMEIELEKSGSLGLSLAGNKKDRSRMSVFVIGDPNGAAG KDGRLLQADELLHNGQILYGRSHQNASIIKCAPSKVKIIFIRNKD AVNQ
MUPP1	2104784	9	LSSFKNVQIHELKPDQGGGLGIAISEEDTLGVIKSLTEHGVAAT DGRLLKVGQDQLAVDDIIVGYPIEFISLLKTAKMTVVKLTTHAEN PDSQ
MUPP1	2104784	10	LPGETTIEISKGRITGLGLSTVGGSDTLGAIHIEVEYEEGAACKD GRLWAGDQILEVNGIDRLKATHDEAINVLRQTPQVRVLTLYRD EAPYKE
MUPP1	2104784	11	KEREVCDTLTIELQKKPGKGLGLSIVGKRNDTVGVFSDIVKGGA DADGRLLMQGDQILMVNGEDVRNATQEAVALLEKCSLGTVTLE VGRKAGPFHS
MUPP1	2104784	12	LQGLRTVEMKKGPTDSLGSIAAGGVGSPGLDVPFIAMMHPTGV AAQTQKLRVGDRIVTICGTSTEGMTHTQAVNLLKNASGSIEMQ VVAGGDVSV
MUPP1	2104784	13	LGPPQCKSITLERGPDGLGFSIVGGYGSHPGDLPIYKTVFAKGA ASEDGRLLKRGDQIIAVNGQSLGVVTIERAVAILKRTKGTVTLMV LS
NeDLG	10863920	1	IQYEEIVLERGNSGLGFSIAGGIDNPHVPDDPGIITKIIPGAAAM DGRIGVNDVCLRVNEVESEVVHSAVBALKEAGFVVRVLRV RRQN
NeDLG	10863920	2	ITLLKGPGLGFSIAGGIGNQHPIGDNSIYITKIEGGAQKDGRL QIGDRLLAVNNNTNLQDVRHEEAVASLKNTSDMVLYKVAKPGSL E
NeDLG	10863920	3	ITLLHKGSTGLGFNTVGGEDGEGIFVSPILAGGPADLSGELRRGDRI LSVNGVNLNRLNATHEQAAAALKRAGQSVTVAQYRPEEYSRFE KIHDLREQMMNNSMSSGSGSLRTSEKRSLE
Neurabin II	AJ4011891	1	CVERLELPVIELEKDSBGLGISIIMGAGADMGLEKLIGFVKTVT EGGAHRDGRIGVNDLLVEVDGTLVGVVTSQFAASVLRNTEKGR VRFMIGRERPGEQSEVAQRIIRD (SEQ ID NO:247)
NOS1	642525	1	IQPNVISVRLFKRKVGGLGFIKVERVSKFPVIEDLRGGAAEQSG LIQAGDILAVNGRPLVDLSYDSALEVLRGASETHVVLIRGP
novel PDZ gene	7228177	1	QANSDESDIHSVRVEKSPAGRLGFSVRGGSEHGLGIFVSKVEEG SSAERRAGLCVGDKITEVNGLSLESTTMGSAVKVLTSSRLHMM VRRMGRVPGIKFSKEKNSS

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novel PDZ gene	7228177	2	PSDTSSSDGVRRIVHLYTTSDDFLGFINIRGGKEFGLGIYVSKVD HGGLABENGKIVGDQVLAANGVRFDDISHSQAIVFLKGQTHM LTIKETGRYPAYKEMNSS
Novel Serine Protease	1621243	1	KIKKFLTSHDRQAKGKAITKKYIGIRMMSLTSSKAKBLKDRH RDFPDVISGAYIEVDPDPAEAGGLKENDVIISINGQSVVSANDV SDVIKR8STLNMVVRGNEIDMITV
Numb Binding Protein	AK056823	1	PDGETSIKINRVPDSBSLSIRLVGGSEITPLVHHIHIYRDGVARD GRLLPGDIIILKVNMGDISNVPHNYAVRLRLQPCQVWLVTMRE QKFRSRNSS
Numb Binding Protein	AK056823	2	HRPRDDSPFVILNKSSPEBQLGIKLVKVDPEPGVFENVLDGGVA YRHQGLEENDRVLAINGHDLRYGSPESAHLQASERRVHLVVS RQVRQRSPENSS
Numb Binding Protein	AK056823	3	PTTTCHEKVYVNIQKDPGESLGMTVAGGASHREWDLPIYVISVEP GGVISRDGRIKTGDILLNVDDGVELTEVSRSEAVALLKRTSSIVL KALIEVKEYPEQETIV
Outer Membrane	7023825	1	LLTEEHNLTRGSPGLGFNIVGGTDQQYVSNDSGIYVSRIKENG AALDGRLEQDGKILSVNGQDLKNLHQDAVDLFRNAGYAVSL RYOHRLOVQNGIHS
p55T	1273367	1	PVDAIRILGIEKRAEPLGVTFRVENNDLVIAIRLHGGMIDRQGL LHVGDIIKEVNGHEVGNPNKELQELKNISGSVTLKILPSYRDTIT PQQ
PAR3	8037914	1	PNFSLDDMVKLVEVPNDGGPLGHVVPFVSARGRTLGLLVKRL EKGGKAHEHNLFRENDCIVRENDGDLNRNRFQAOHMFRAQMR IPIHWFHVPPAANKQEYEQ
PAR3	8037914	2	GKRLNIQLKKGTGELGFSITSRDVTIGGSAPIYVKNLPRGAAIQD GRLLKAGDRLEIVNGVDLVGKSQEEVVSLLRSTKMEGTVSLVP RQEDA
PAR3	8037914	3	PREFLTFEVPLNDSSGAGLGVSVKGNRSKENHADLGIFVKSING GAASKDGRRLVNDQLIAVNGESLIGKTNQDAMETLRRSMSTEG NKRGMIOQLIVASRISKCNELKSNSS
PAR3-like 0	AF42825	1	PRTKDITLSDMTTRTVEISGEGPLGIHVVPFSSISGRILGLFIRGIE DNSRSKREGFLFIENECIVKINNVDLVDKTFAQAQDVFRQAMKS PSVLLHVLPPQNR
PAR3-like 0	AF42825	2	SNKNAKKIKIDLKKGPBGLGFTVVTTRDSSIHGGPPIFVKNLPKG AAIKDGRLGSGDRILEVNGRDVTRQBELVAMLESTKQGETA SLVIARQEGH
PAR3-like 0	AF42825	3	ITSBQITFEPLNDSSGAGLGVSLLKGNKSRETGTDLGIFKSIHGG AAFKDGRRLMNDQLIAVNGESLIGKSNHEAMETLRRSMSMEG NIRGMIOQLVILRRPFP
PAR6	2613011	1	PETHRRVRLHKGSDRPLGFYIRDGMSVRVAPQGLERVFGIFSR LVRRGLAESTGLLAVSDEILEVNGIEVAGKTLDDQVTDMMVANS ENLIVTVKANQRNNVNSS
PAR6 BETA	13537116	1	PVSSIIDVDILPETHRRVRLYKYGTEKPLGFYIRDGSSSVRTPEGL EKVPGIFISRLVPGGLAQSTGLLAVNDEVLEVNGIEVSGKSLDQV TDMMIANSRLNITVRPANQRNNIHRD
PAR6 GAMMA	13537118	1	IDVDLVPETHRRVRLHRCCEKPLGFYIRDGASVRVITHGLEKV PGIFSRMVPGLAESTGLLAVNDEVLEVNGIEVAGKTLDDQVTD MMMIANSRLNITVRPANQRNNV
PDZ-73	5031978	1	RSRKLKEVRLDRLEPEGLGLSVRGGLEFGCGFLFISHLKGGQAD SVGLQVGEIVRINGYSISSCTHEEVNLIRTKETVSIKVRHIGLIP VKSSPDEFH

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PDZ-73	5031978	2	IPGNRENKEKKVFISLVSGRGLGCSISSGPIQKPGIFISHVKPGSL AEVGLIGDQIVEVNGVDFSNLDHKEAVNVLKSSRLTISIVAAA GRELFMTDEF
PDZ-73	5031978	3	PEQIMGKDVRLRLRIKKEGSLDLALEGGVDSPIGKVVSAYYER AAERHGGIVKGDEIMAINGKIVTDYTLARADAALQKAWNQG DWIDLVAVCPPKEYDD
PDZK1	2944188	1	LTSTFNPRECKLSKQBGQNYGFFLRIEKDTBGLHVRVVEKCS PAEKAGLQDGRVLRINGVFDKBEHMVQVVDLVRKSGNSVTLLV LDGDSYEKAGSPGHIRD
PDZK1	2944188	2	RLCYLVKEGGSYGFSKTVQKKGVYMTDITPQGVAMRAGVL ADHDLIEVNGENVEDASHEEVVEKVKSSGRVMTFLVDKETDK RHFIVTD
PDZK1	2944188	3	QFKRETASLKJ.J.PHQPRIVEMKKGSGNGYGFYLRAGSEQGQIK DIDSGSPAEAGLKNNDLVAVNGESVETLDHDSVVMIREKGG DQTSLLVVDKJTDNMVYLAEEFVTD
PDZK1	2944188	4	PDITIEVDHKKPKLRLAKGNGYGFHLNAIRGLPGSFKEVQKG GPADLAGLEDEDVIEVNGVNVLDPEYKVVDRIOSSGKNVTLL VZGKNSS
PICK1	4678411	1	PTVPGKVTLQKDAQNLIGISIGGGAQYCPCLYTVQVFDNTPAAL DGTVAAGDEITGVNGRSIKGKTKVEVAKMQEYKGEVTHYINK LQ
PIST	98374330	1	SQGVGPRIKVLILKEDHEGLGISITGGKEHGVPLISEIHPGPAD RCGLHLVGDAILAVNGVNLRDITKHKEAVTILSQQRGEIEFVY VAPEVDS
prIL16	1478492	1	IHVTLHKKEGAGLGFSLAGGADLENKVIIVHVFNPGLASQEG TIQKGNEVLSINGKSLKGTTHDAILRLQAREPRQAVITVRELT FEFFIVTD
prIL16	1478492	2	TABATVCTVILEKMSAGLGFSLGEGKSLHGDKPLTINRFGA ASBQSETVQPGDEILQLGGTAMQGLTRFEAWNUIKALPDGPFVTV IRKSLQSK
PSAP	6409315		IREAKYSGVLSSIGKIFKEEGLLGFVGLPHLLGDVFLWGCNL LAHFNAYLVDSVSDTPGGLGNDQNGSQFSQALAIRSYTKFV MGIAVSMLTYPELLVGDLMVANNCLQAGLPPYSPVFKSWIHC WKYLSVQQLFRGSSLLFRYSSGSCFALE
PSD95	3318652	1	LEYBFTLERGNSGLGFSIAGGTDNPHIGDDPSIFITKIIPGAAAQ DGLRLVNDNISLTVNEVDVREVTHSAVAALKKAGSIVRLYVYMR EKPPAENSS
PSD95	3318652	2	HVMRRKPPAEKVMETIKLIKPKGLGFSIAGGVGNQHIFGDNSTY VTKIEGGAHKGDRLOQDKILAVNSVGLDEDVMEHDAVAALK NTYDVVYLKVAKPSNAYLLEFIVTD
PSD95	3318652	3	RERHTPRTEANCDSRGSTGLGFNIVGGEDGEGILSPISWPALQ TSVSGCGRGTRSCRSTVTWTEMPAMSRLLP
PTN-3	179912	1	QNDNGDSYLVLRITPDEDGKGFNLKGGVDQKMPLVVSRINPE SPADTCIPKLNBDQVILNGRDISEHTHDQVVMFKASRESHSR ELALVIRRAVRS
PTN-4	190747	1	IRMKPDENGRFGFNVKGGYDQKMPVIVSRVAFPTADLCVPL NEGDQVVLNGRDIAEHTDQVVLFIKASCRHSGLMLLVRPN A
PTPL1	515030	1	PERHTLVNLKKDAKYGLGFQIGGEKMGRLDLGFISSVAPGGP ADFHGCLKPGDRILSVNSVSLGVSETHAAIEILQNAPEDVTLVIS QPKKISKVPSTPVL

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PTPL1	515030	2	GDIFEVELAKNDNSLGISVTGGVNTSVRHGGHYVKA VIPOGA AE SDGRIHKDRLVLA VNGVSLGATHKQAVETLRNTGQV VHHLL E KGQSPTS K
PTPL1	515030	3	TEBNTFEVKLFKNSSGLGFSFREDNLPEQINASIVRVKKLIFAGQ PAAESGKIDVGDVILK VNGASLKLGSQQEIVSALRGTAPEVFL L CRPPPGVLPEDT
PTPL1	515030	4	ELEVE LLITLIKSEKASLGFTVTKGNQRIGCVYHVDIQDPAKSDG RLKPGDRILK VNDTDVNTMTETDA VNLRAASKTVRLVIGRV L ELPRIPMLPH
PTPL1	515030	5	MLPHLLPDITLTCNKBELGFSLCGGHDSLYQVVVISDINPRSVAA TEGNTQLLDVIHYVNGVSTQGMILEBVNRALDMSLP SLVLKAT RNDLPV
RGS12	3290015	1	RPSPPRVRSVEVARGRAGYGF T LSGQAPCVLSCVMRGSPAD FV GLRAGDQILAVNEINVK KASHEDVVKLGKCSGVLHMVIAEGV GRFESCNS S
RGS3	18644735	1	LCSERRYRQITPGRKDGFGFTICDSPVRVQAVDSGGFAERAGL QQLD TVLQLNRPVEHWKCVELAHEIRSCPSEIILLVWRMVPQV KPGIHRD
Rho-GAP 10	NM020821 4	1	SEDETFSPWPGPKTVILKRTSQGFGLTRHPTVYPPEAIQFSYKD EENGNRGGKQRNRLPMDTIFVKVQVKEGGPAFEAGLCTGDRIK VNGESVIGKTYSQVIALIQNSDTTLEL SVMPKDED
Rhopilin-like	14279408	1	SAKNRWRVLVGPVHLTRGEGGFLTLRGDSPVLIAAVIPGSQAAA AGLKBGDYIVSVNGQPCRWRRHA EVVTELKAAAGEAGVQV V SLPSSRLPSI
Serine Protease	2738914	1	RGEKKNSSSGISGSRRYIGVMMILTSPLSIALQLREPSPDVQ HGVLIHKVILGSPAHRAGLRPGDVILAIGEQMVQNAEDVYEA VR TQSQLA VQIRRGREITLY VNSS
Shank 2	6049185	1	LEBKT VVLQKKNBGGFGFVLRGAKADTPIEBFTPTAPFALQYL ESVDEGGVAWQAGRLTGDFLIEVNNENNVVKVGHQRQVVMIRQ GGNHLVLKVVTITRNLD PDDNSS
Shank 3	*	1	SDYVIDDKVAVLQKRDEHGFGLRGAKAETPIEBFTPTAPFA LQYLESVDVEGVAWRAGLRITGDFLIEVNGVNVVKVGHKQVVA LIRQGGNRLVMKVVS VTRKPBEDG
Shroom	18652858	1	ISNTATKGRYTYLEAFLEGGA PWGFTLKGGLHEHGEPLISKVEEG GKADITSSKLQAGDEVVHINEVTLSRSREKAVSLVKGSYKTLRL VVRDVCIDPGHAD
Similar to GRASP65	14286261	1	MGLGVSAEQPAGGAEGFHLHGVOENSPAQQAGLEPYDFDITIG HSRLNKENDTLKALLKANVEKPVKLEVNMTKRVREVEVVP SNMWGGQGLIGASVRCFSRRASE
Similar to GRASP65	14286261	2	RASEQVWHVLDVEPSSPAALAGLRPYTDYVVGSDQLQESDEDF TLIESHEGPKPLMVVYNSKSDSCRSBGMWHWLWYSTDPNSAP QLPQEATWHPTTFCSITTWCPTT
Similar to Ligand of Numb px2	BC036751 5	1	IQPLSLPEGEITTIHRSNFPYQLGISIVGGNETPLINTVQEVYRDG VIARDGRLLAGDQILQVNNYNISNVSHNYARAVLSQPCNTLHLT VLRRERFGRNAH
Similar to Ligand of Numb px2	BC036752 5	2	SNSPREETQVALHKRDSGEQLGIKLVRRITDEPGVFLDLL EGG L AAQDGRILSSNDRVLAINGHDLKYGTPELAAQHQASGERVNLIT ARPGKPPQG
Similar to Ligand of Numb px2	BC036753 5	3	QCVTQCEKHITVKKEPHESLGMTVAGGRGSKSGELPIFVTSVPP HGCLARDGRIGRGDVLINNGIDITNLSSHSEAVAMLKASASPA VALKALBVQIVBEAT

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Similar to Ligand of Numb p22	BC036755	4	PS TLHSCHDIVLRRSYLGSWGFSIVGGYEEHNHTNPQFFIKTIVLG TPAYYDGR LKCGDMIVAVNGLSTVGMSSHSLVPMLEKQRNKV TLTVICWPGS
Similar to PTP Homolog	21595065	1	SVTDGPKFEVKLKKNANGLGFSFVQMEKESCSHLKSDLVRIKRL FPGQPAEENGAIAGDILAVNGRSTBGLIFQEVHL LLRGAPOQEVILLCRPPFGA
SIP1	2047327	1	QPEPLRPRLCRLVRGEQGYGFHLHGEKGRRGQFIRRVPEGPSAE AAALRAGDRLVEVNGVNVGEETHQVVRKIAVEGQTRLVV DOETDEELRRRNS
SIP1	2047327	2	PLRELPRLCRLKGPQGYGFNLHSDKSRFGQYIRSVDPGPSAA RSGRLAQDRLIEVNGQNVGELRHAEEVVASIKAREDEARLLVVD PETDEHFKRNS
SITAC-18	8886071	1	PGVREIHLCKDERGKTGLRLKVDQGLFVLQVQANTPASLVGL RFGDQLLQIDGRDCAGWSSHKARQVVKKASGDKIVVVRDRP FORTVTM
SITAC-18	8886071	2	PPQRTVTMHKDSMGHVGFVIKKGKIVSLVKGSSAARNGLLTNH YVCEVDGQNVIGLKDKKIMEILATAGNVVTLTIPSVIYEHVEFI V
SNPCIIA	20809633	1	SLERPRFCLLSKEEGKSFGFHLQQLGRAGHVVCRVDPGTSAGR QQLQEGDRILAVNNDVVEHEDYAVVVRIRASPRVLLTVLAR HAHDVARAQ
SNPCIIA	20809633	3	ISLPTKPRCLHLEKGPQGGFLLREBKGLDGRPGQFLWEVDPGL PAKKAAGMQAGDRLVAVAGESVEGLGHETVSRIGQGQSCSVSLT VVDPEADR
SNPCIIA	20809633	4	IPSVPLGSRQCFLYPGPGSGYGFRLSCVASGPRFLFISQVTPGSSA ARAGLQVGDVILEVNGYVPVGGQNDLERLQQLPEAPEPLCLKLA ARSLRGL
Shank1	7025450	1	LKEKTVLLQKKDSEGGFVLRGAKAQTHIEFTPTAPFALQYLE SVDEGGVAWRAGLRMGDFLIEVNGQNVVKGVGHQVQVNMIRQ GGNTLMVKVVMVTRHPDMDEAVQNS
SYNTENIN	2795862	1	LEIKQGIREVILCKDQDGKIGLRLKSIDNGIFVLQVANSASLV GLRFGDQVLQINGENCAGWSSDKAHKVLKQAFGEKTMRIHRD
SYNTENIN	2795862	2	LRDRPFERTITMHKDDSTGHVGFIFKNGKITSIVKSSAARMGLLT EHNICEINGQNVIGLKDSQADLSTSGTVVTTMPAFIEHNMNS
Syntrophin alpha	1145727	1	QRRRVTVVRKADAGGLGISKGGRENKMPILISKIFGLAADQTE ALFVGDAILSVNGEDLSATHDEAVQLKKTGKEVVLVVKYMK DVSPYFK
Syntrophin beta 2	476700	1	PVRRVVKQEAAGLGISIKGGRENKMPILISKIFPGLAADQSRALR LGDAILSVNGTDLRQATHDQAVQALKRAGKBTLLVFKFIRE
Syntrophin gamma 1	9507162	1	EPFYSGERTVTRRQTVGGFGLSIKGGAEHNIPVVVSKISKQRA ELSGLLFIGDAIQINGINVRKCRHEEVVQVLNAGEBVLTVSF LKRAPEFLKLP
Syntrophin gamma 2	9507164	1	SHQGRNRRVTILRRQPVGGGLGSIKGGSEHNVPVVISKIFEDQA ADQTGMLFVGDAVLQVNGHEVENATHEBVVHLLRNAGDEVITIT VEYLRRAPAEFLK
TAX2-like protein	3253116	1	RGETKEVEVTKTETDALGLTIDNGAGYAFIKRIKESHNRIEAVC VGDSIBAINDSIVGCRHYEVAKMLRELKPSQPFITLRLVQPKRA F
TIAM 1	4507500	1	HSIHIEKSDTAADTYGFSLSVVEEDGIRRLYNVSKETGLASKKG LKAGDEILENNRAADALNNSMTKDFLSQPSLGLLVRTYYPELE
TIAM 2	6912703	1	PLNVYDVQLTKGSCDTPGFAVTAQVDIRQLSRIFSDVLPDG LAYGRLGRKNGEIMTLNGEAVSDLDLQMEALFSEKSVGLTLIA

Gene Name	GI or Acc#	PDZ#	Sequence fused to GST Construct
			RPPDIKATL
TIP1	2613001	1	QRVEIHKLRQGENLILGFSIGGGIDQDPSONFFSEDKTKDGIYVT RVSEGGPAEIAGLQIGDKIMQVNGWDMTMVTHDQARKRLTKR SEEVVRLLVTRQSLQK
TIP2	2613003	1	RKEVEVEKSEDALGLTITDNGAGYAFIKRIKESVIDHIHLSVGD MIBAINQSSQLGCRHYEVARILKELPRGRTFTTLKLEPRK
TIP33	2613007	1	HSHPRVVELPKTDEGLGFNVMGKGKQNSPIYSRIIPGGVAERHG GLKRGDQLLSVNGVSVGEHHEKAVELLKAADSVKLVRVRYT PKVL
TIP43	2613011	1	LSNOKRGVVKVLKQELGGLGISIKGGKKNKMPILISKIFKGLAADQ TQALYVGDAILSVNGADLRDATHDEAVQALCRAGKRVLLEVK YMRBATPYVKNS
Unknown PDZ gene		1	QRSSIKTVELIKGNLQSVGLTLRLVQSTDYAGHVHETVAPNSP AAIADLQGRDLIAIGGVKITSTLQVLKLIKQAGDRVLVYYERP VGQSNQGA
X-11 beta	3005559	1	IHFSENSENCKELQLEKHKGEILGVVVVSESGWSILPTVILANMM NGGPAARSCKLSIGDQIMSINGTSLVGLPLATCQGIKGLKNQQTQ VKLNIVSCPPVTVTLKRNSS
X-11 beta	3005559	2	IPPVTVTLKRPDLKYQLGFSVQNGHCSLMRGGAERGVRVGH RIIBINGQSVVATAHEKIVQALSNSVGEIHMKTMPAAMFRLLTG QENSS
ZO-1	292937	1	IWEQHTVTLHRAPGFGFGIAISGGRDNPFPQSGETSIVISDV LKO QPAEGQLQENDRVAMVNGVSMNDNVEHAFVQQLRKSGKNAKI IIRKKKKVQIPNSS
ZO-1	292937	2	ISSQPAKPTKVTILVSKRNKEEYGLRLASHIFVKEISQDSLAARDG NIQEGDVVLKINGTVTENMSLTDAKTLIIRSRKGLKVMVVRQDR ATLLNSS
ZO-1	292937	3	IRMKLVKFRKGDSVGLRLAGGNDVGIFVAGVLEDSPAAGEGLE EGDQILRVNNVDFTNIREEAVLFLDLPLKGBEVTILAQKKKDV SN
ZO-2	12734763	1	LIWEQYTVTLQKDSKRGFGIAVSGGRDNPFPENGETSIVISDVLP GGPADGLLQENDRVVMVNGTPTMEDVLHSAFVQQLRKSGKVA IVVKRPKRV
ZO-2	12734763	2	RVLLMKSRANEEYGLRLGSIQIFKEMTRTGLATKDGNLHEGDII LKINGTVTENMSLTDARKLIEKSRGKLQLVLRIS
ZO-2	12734763	3	HAPNTKMVREKKKGDSVGLRLAGGNDVGIFVAGIQEGTSABQBG LQEGDQLKVNQDFRGLVRDEAVLYLLEIPKGBMVTILAQSRA DYY
ZO-3	10092690	1	IPGNSTIWBQHTATLSKDPRRGFGIAISGGRDRPGGSMVVSDDVP GGPAEGRLQTGDEHVMVNGVSMENATSAFAIQLEKCTCKMANIT VKRPRIHLPAAEFTVD
ZO-3	10092690	2	QDVQMKPVKSVLVKCRDSEEFVKLGSIQIFKHTDLSGLAARHR GLQEGDLILQINGVSSQNLSLNDRRLIEKSBGKLSLLVLRDRGQ FLVNIPNSS
ZO-3	10092690	3	RGYSPDTRVVRFLKSGSIGRLAGGNDVGIFVSGVQAGSPADG QGIQEGDQLQVNDVFPQNLTRREAVQTLGLLPPGEEMELVTQR KQIDFWKMWQSEFTVD

*: No GI number for this PDZ domain containing protein - it was computer cloned by J.S. using rat Shank3 seq against human genomic clone AC000036. In silico spliced together nt6400-6496, 6985-7109, 7211-7400 to create hypothetical human Shank3.

Vectors: All PDZ domain-containing genes were cloned into the vector pGEX-3X (Amersham Pharmacia #27-4803-01, Genemed Aco#U13852, GH#595717), containing a tac promoter, GST, Factor Xa, β -lactamase, and lac repressor.

The amino acid sequence of the pGEX-3X coding region including GST, Factor Xa, and the multiple cloning site is listed below. Note that linker sequences between the cloned inserts and GST-Factor Xa vary depending on the restriction endonuclease used for cloning. Amino acids in the translated region below that may change depending on the insertion used are indicated in small caps, and are included as changed in the construct sequence listed below.

10 aa 1 - aa 232:

MSPLIGYWKIKGLVQPTRLLLEYLEEKYEBHLYERDEGDKWRNKKFELGLEFPNLPY
YIDGVDKLTQSMAIRYIADKHNMLGGCPKERAISMLEGAVLDIRYGVSR IAYS KDF
ETLKVDFLSKLPEMLKMFEDRLCHRTYLN GDH VTHPDFMLYDALDVVLYMDPMCL
DAFFKLVCFFKRIHAIPQIDKYLKSSKYIAWPLQGWQATFGGGDHPPKSDLIEGRgipg

15 nss

Constructs: The preparation of the construct for RIM2 (KIAA0751) is exemplified as flows. Constructs of the PDZ domains in Table 3 were prepared by similar methods. Primers used to generate RIM2 DNA fragments by PCR are listed in Table 4. PCR primer combinations and restriction sites for insert and vector are listed below, along with amino acid translation for insert and restriction sites. Non-native amino acid sequences are shown in lower case.

TABLE 4

Primers used in cloning of RIM2 PDZ domain 1.

ID# (Primer Name)	Primer Sequence	Description	Seq ID
1968 (688KIFlo)	AAAGATCTCCCTTA ACGAGGAGCATAG	Forward (5' to 3') primer corresponding to RIM2, domain 1. Generates a BglII site upstream (5') of the PDZ boundary. Used for cloning into pGEX-3X.	273
1093 (319 KIR)	GAACAATTGCAATA GGCCTTGAACTAC	Reverse (3' to 5') primer corresponding to RIM2, domain 1. Generates a MfeI site	274

ID# (Primer Name)	Primer Sequence	Description	Seq ID
		downstream (3') of the PDZ boundary. Used for cloning into pGEX-3X.	

RIM2, PDZ domain 1: GI#: 12734165; Construct: RIM2, PDZ domain 1-pGEX-3X; primers: 1968 & 1093; Vector Cloning Sites (5'/3'): Bam HI/EcoRI; Insert Cloning Sites(5'/3'): BglII/MfeI

5 aa 1- aa 126

TLNEEHSHSDKHPVTWQPSKDGDRLIGRILLNKRDKGSVPRDSGAMILGLKVVGKK
MTESGRLCAPITKVKKGLADTVGHLPQDEVLEWNGRLIQGATFEBVYNILESKP
EPQVELVVSRIPIG

GST Fusion Protein Production and Purification: The constructs using pGEX-3X expression vector were used to make fusion proteins according to the protocol outlined in the GST Fusion System, Second Edition, Revision 2, Pharmacia Biotech. Method II and optimized for a 1L LGPP.

Purified DNA was transformed into *E.coli* and allowed to grow to an OD₆₀₀ of 0.4-0.8 (600λ). Protein expression was induced for 1-2 hours by addition of IPTG to cell culture. Cells were harvested and lysed. Lysate was collected and GS4B beads (Pharmacia Cat# 17-0756-01) were added to bind GST fusion proteins. Beads were isolated and GST fusion proteins were eluted with GEB II. Purified proteins were stored in GEB II at -80°C.

Purified proteins were used for ELISA-based assays and antibody production.

Example 7: Identification of PDZ Domains Bound by the C-terminus of MUC1

Summary: To determine the human PDZ domains bound by the C-terminus of MUC1, peptides corresponding to the PL (20 amino acids of the C-terminus (SEQ ID NO: 96) or 9 amino acids of the C-terminus coupled to 11 amino acids of the TAT transporter (SEQ ID NO: 102) were synthesized and purified to >95% by HPLC. These peptides were assessed for binding to individual GST-PDZ domain fusion proteins using the modified ELISA describe below. Interactions giving higher absorbance values in the assay were titrated to determine relative EC50 values.

Reagents and Supplies:

Nunc MaxiSorp 96 well Immuno-plate, Nunc;

PBS pH 7.4 (phosphate buffered saline, 8g NaCl, 0.29g KCl, 1.44g Na_2HPO_4 , 0.24g KH_2PO_4 , add H_2O to 1L and pH 7.4; 0.2 μ filter) Assay Buffer: 2% BSA in PBS (20g of bovine serum albumin per liter PBS, fraction V, ICN Biomedicals, cat#IC15142983

Goat anti-GST polyclonal Ab, stock 5 mg/ml, stored at 4°C, Amersham Pharmacia cat#27-

5 4577-01;

Dilute 1:1000 in PBS, final concentration 5 μ g/ml;

HRP-Streptavidin, 2.5mg/2ml stock stored at 4°C, Zymed cat#43-4323, dilute 1:2000 into Assay buffer, final [0.5 μ g/ml]

Wash Buffer, PBS;

10 Biotinylated peptides (HPLC purified, stock solution store in -20°C freezer #7)

GST-PRISM proteins (stock stored at -80°C, after first thaw store in -10°C freezer #7)

TMB (3,3',5,5', tetramethylbensidine), tablets, Sigma cat.#T5525;

Per plate, dissolve 1 tablet in 1mL DMSO, add 9mL Citrate/Phosphate buffer pH 5.4 and 2 μ L H_2O_2 ;

15 0.18M H_2SO_4 , Sigma cat.#S1526;

12-w multichannel pipettor & tips;

50 ml reagent reservoirs, Costar#4870;

50, 15 ml polypropylene conical tubes;

Costar Transtar 96 Costar#7605;

20 Transtar 96 Cartridge Costar#7610;

Cluster tubes;

Molecular Devices microplate reader (450 and 650 nm filters);

SoftMax Pro software;

When using reagents stored at or 4°C or -20°C, remove and keep on ice

25 Protocol:

Coat plate with 100 μ l of 5 μ g/ml anti-GST, O/N at 4°C;

Dump contents of plate & out tap dry on paper towels;

Block with 200 μ l Assay Buffer for 2 hrs at room temperature;

Prepare proteins in Assay Buffer;

30 Wash 3X with cold PBS*;

Add proteins at 50 μ l per well, incubate 1 to 2 hrs at 4°C;

Prepare peptides in Assay Buffer;

Wash 3X with cold PBS*;

Add peptides at 50 μ l per well on ice (write time on plate);
 Incubate on ice after last peptide has been added for exactly 10 minutes;
 Place at room temp for exactly 20 minutes;
 Prepare HRP-Streptavidin within 10 minutes of time of use;

- 5 Promptly wash 3X with cold PBS;
 Add 100 μ l per well of HRP-Streptavidin (write time on plate);
 Incubate at 4°C for exactly 20 minutes;
 Turn on plate reader and prepare files;
 Promptly wash 5X with PBS at room temperature;
- 10 Add 100 μ l/well TMB substrate (write time on plate);
 Incubate in dark at room temp for a maximum of 30 minutes;
 Read plate at 25 minutes (650 nm);
 Stop reaction with 100 μ l of 0.18M H₂SO₄, 30 min. after adding TMB;
 Take last reading at 450 nm soon after stopping reaction;
- 15 * do not let plates dry out

Profile Results: Peptides corresponding to the C-terminus were able to bind a number of PDZ domains in a concentration dependent manner. FIG. 3 shows the results of MUC1 binding to individual PDZ domains at a MUC1 peptide concentration of 0.01 μ M, and seven interactions are observed to give higher absorbance readings in the assay. When the concentration of MUC1 peptide is increased to 0.1 μ M, more interactions are observed (FIG. 4). Identities of the interacting PDZ domains are listed directly above or next to the bar representing the absorbance in the assay.

Titration to determine relative EC₅₀ values: Peptide corresponding to MUC1 was then titrated against a constant amount of the PDZ domain-containing recombinant proteins identified in the first part of this example. From these, relative EC₅₀ values are listed in Table 4 indicating the concentration of MUC1 peptide for 50 percent binding to the indicated PDZ domain

Table 4

PDZ	EC50 μ M
Lim Mystique	0.010
SP1 d1	0.011
AIPC1	0.014

PDZ	EC50 μ M
KIAA0751	0.016
ZO-1 d2	0.019
SITAC 18	0.026
NSP	0.027
MAST d2	0.039
Pril-16 d1	0.041
KIAA1526 d1	0.051
GRIP2 d5	0.060

The C-terminus of MUC1 clearly functions as a PDZ ligand and several PDZ domains can bind to the MUC1 C-terminus, and modulation of these interactions provide a point of therapeutic intervention.

5 Example 8: Expression of PDZ Domains in Human Cancer Cells

Expression of PDZ domains in breast cancer cell lines was examined using quantitative PCR to confirm that PDZ domains shown to interact with the C-terminus of MUC1 are present in cancer cell lines.

- Methods: cDNA was prepared from 4 cell lines using standard methods: human
10 breast cancer MCF-7 cells; human breast cancer ZR-75 cells; human colon cancer HCT116 cells transfected with MUC1; human colon cancer HCT116 cells transfected with vector as a control. HCT116 cells do not express MUC1 endogenously. MUC1 transfection of HCT116 cells is described in U.S. Patent Application Publication 2004/0018181 A1, incorporated herein by reference. Amplicon primer pairs were designed using software provided with our
15 ABI7000 Real Time PCR machine. Reactions performed in duplicate, and were repeated independently.

- Cells were grown under respective growth conditions to 80% confluency. Total RNA was isolated using TRIZOL and standard protocols. cDNA was generated by using Superscript Reverse Transcriptase and random primers (Invitrogen). Real time PCR was
20 performed on the cDNAs utilizing the SYBR GREEN method (ABI) and quantified in an ABI PRISM 7000 Sequence detection system. Relative expression is based on copy numbers for an EGFR Plasmid/Amplicon primer pair which was used for a standard curve (from 1 million to 320 copies) which was included in each individual plate. Values >200 were considered significant over background. Also included in each plate was a beta-Actin control

- for each of the four cell types. Minus RT controls were also included and each individual plate contained a non-template control using beta-Actin primers. Amplicon primers were designed using the ABI Primer Design software and corresponded to sequences within the respective hit-PDZ except for MINT-3 where a sequence outside the PDZ domain was used.
- 5 Reactions were done in duplicates and for all genes which showed no expression, a second independent primer pair within the PDZ sequence (except for MINT-3) was designed and checked against the cDNAs. In addition, each negative primer pair was checked against the respective PDZ Plasmid to confirm whether the primer pair is functional. For all primer pairs except for the GRIP-2 primers functionality was confirmed with the Plasmids. Table 5 shows
- 10 the primers used to determine PDZ gene expression in ZR-75, MCF7 and HCT116 +/- MUC1 transgene expression cell lines.

Table 5
Oligonucleotide primers used for RT-PCR

AVC		Sequence	Description
No	Oligo Name		
3303	Zo-3 dom3 FA	gcatccaggaggagatcag	forward amplicon primer
3302	Zo-3 dom3 RA	aggctctggaatggcagtc	reverse amplicon primer
3301	Zo-3 dom3 FB	gggcatccaggaggagat	forward amplicon primer
3300	Zo-3 dom3 RB	caggctctggaatggcagc	reverse amplicon primer
3299	Zo-3 dom1 FA	caggcgaccacatgctcat	forward amplicon primer
3298	Zo-3 dom1 RA	gaggtggcattctccatgga	reverse amplicon primer
3297	Zo-3 dom1 FB	tccatggagaatgccacctc	forward amplicon primer
3296	Zo-3 dom1 RB	ccatcttggtgcaaggcttga	reverse amplicon primer
3295	Zo-2 dom1 FA	agtgtctcatgtccaatggca	forward amplicon primer
3294	Zo-2 dom1 RA	gcaaacgaatgaagcacatcc	reverse amplicon primer
3293	Zo-2 dom1 FB	cigtgggtgctcccaaga	forward amplicon primer
3292	Zo-2 dom1 RB	gggtgccattgaccatgac	reverse amplicon primer
3291	Zo-2 dom2 FA	agtatgtctccggttggg	forward amplicon primer
3290	Zo-2 dom2 RA	ttogggcatcttcttaaga	reverse amplicon primer
3289	Zo-2 dom2 FB	gatgaaaagcagagcagaaga	forward amplicon primer
3288	Zo-2 dom2 RB	cgaagatgtgactcccaagoo	reverse amplicon primer
3252	KIA0340 DOM 1 2ND R	caccaagtgctctaatgagtcac	reverse amplicon primer
3251	KIA0340 DOM 1 2ND F	tgggtgtgaaagtgtgtgagg	forward amplicon primer
3250	GRIP2 DOM 5 2ND R	cagttgkcaggcggatattg	reverse amplicon primer

AVC			
No	Oligo Name	Sequence	Description
3249	GRIP2 DOM 5 2ND F	ggagccaaggcgacaago	forward amplicon primer
	LIM MYST DOM 1 2ND		
3248 R		cgttgatggccaogattatgt	reverse amplicon primer
	LIM MYST DOM 1 2ND		
3247 F		aaagccaaggacgctgcact	forward amplicon primer
3246 KIA0316 DOM 1 2ND R		aggagtatagattctttgcagctt	reverse amplicon primer
3245 KIA0316 DOM 1 2ND F		cagagagcgggtcctcagtc	forward amplicon primer
3244 MAG2 DOM5 2ND R		tctaccctcctcctcccaat	reverse amplicon primer
3243 MAG2 DOM5 2ND F		agactggcagaagatggacca	forward amplicon primer
3242 MAST1 DOM 1 2ND R		tccgtgtcaccatgttagacac	reverse amplicon primer
3241 MAST1 DOM 1 2ND F		gaagtatggcttcacactggt	forward amplicon primer
3240 MINT3 COMPL 2ND R		catgctggactccaagct	reverse amplicon primer
3239 MINT3 COMPL 2ND F		cgaattgggaactgcctgaa	forward amplicon primer
3238 MUPP1 DOM 3 2ND R		caatgtagccgaatgtgtaatic	reverse amplicon primer
3237 MUPP1 DOM 3 2ND F		gaactcactaaaaatgtccaggattag	forward amplicon primer
	NOVEL PDZ DOM 1		
3236 2ND R		ccatgggtgtgctctccag	reverse amplicon primer
	NOVEL PDZ DOM 1		
3235 2ND F		gggacaagatcacggagggtg	forward amplicon primer
3234 NSP DOM 1 2ND R		cgtctctgagatcacgtctg	reverse amplicon primer
3233 NSP DOM 1 2ND F		aaagagctgaaggacgggc	forward amplicon primer
3232 HER1 2ND R		tggccatcaagttagcttctc	reverse amplicon primer
3231 HER1 2ND F		agcaacatctccgaagccaa	forward amplicon primer
	SYNTROPHINY DOM 1		
3230 R		tcatgtgttggattcttgaa	reverse amplicon primer
	SYNTROPHINY DOM 1		
3229 F		gcacaacgtccctgtgtctc	forward amplicon primer
3228 PRIL16 DOM 1 R		cgtgtgtcccttgagagactt	reverse amplicon primer
3227 PRIL16 DOM 1 F		aaggcgcaatgaggtttcttc	forward amplicon primer
3226 KIA 1719 DOM 5 R		gcagttgtcaggcggata	reverse amplicon primer
3225 KIA 1719 DOM 5 F		gagccaggcgacaagctact	forward amplicon primer
3224 KIA1526 DOM 1 R		cccgagctctctctctctc	reverse amplicon primer
3223 KIA1526 DOM 1 F		acgtgtctctctgttggaaccag	forward amplicon primer
3222 FGFR3 IIC B NEW R		gcacgtctcagcgtgtacgt	reverse amplicon primer

AVC		
No	Oligo Name	Description
3221	FGFR3 IIC B NEW F	forward amplicon primer
3220	FGFR3 IIC A NEW R	reverse amplicon primer
3219	FGFR3 IIC A NEW F	forward amplicon primer
3218	HER2 B NEW R	reverse amplicon primer
3217	HER2 B NEW F	forward amplicon primer
3216	HER2 A NEW R	reverse amplicon primer
3215	HER2 A NEW F	forward amplicon primer
3214	VARTUL COMPLETE R	reverse amplicon primer
3213	VARTUL COMPLETE F	forward amplicon primer
3212	SITAC18 DOM 1 R	reverse amplicon primer
3211	SITAC18 DOM 1 F	forward amplicon primer
3210	DLG 1 DOM 2 R	reverse amplicon primer
3209	DLG 1 DOM 2 F	forward amplicon primer
3208	DLG 1 DOM1 R	reverse amplicon primer
3207	DLG 1 DOM 1 F	forward amplicon primer
3206	Ubiquitin R Chamorro	reverse amplicon primer
3205	Ubiquitin F Chamorro	forward amplicon primer
3204	Ubiquitin F	forward amplicon primer
3203	Ubiquitin R	reverse amplicon primer
3202	18S KNA R	reverse amplicon primer
3201	18S RNA F	forward amplicon primer
3200	PTPL1 dom4 R	reverse amplicon primer
3199	PTPL1 dom4 F	forward amplicon primer
3198	Mupp1 dom 6 R	reverse amplicon primer
3197	Mupp1 dom 6 F	forward amplicon primer
3196	Mast 3 com 1 R	reverse amplicon primer
3195	Mast 3 dom 1 F	forward amplicon primer
3194	Kia340 dom 1 R	reverse amplicon primer
3193	Kia340 dom 1 F	forward amplicon primer
3192	INADL dom 3 R	reverse amplicon primer
3191	INADL dom 3 F	forward amplicon primer
3190	PAR 3 dom 3 R	reverse amplicon primer
3189	PAR3 dom 3 F	forward amplicon primer
3188	Pick 1 dom 1 R	reverse amplicon primer

AVC			
No	Oligo Name	Sequence	Description
3187	Pick 1 dom 1 F	gggtgcaatggcaggtcaato	forward amplicon primer
3186	RGS3 dom 1 R	gaatccaaggcctggactc	reverse amplicon primer
3185	RGS3 dom 1 F	tgggttcaacatctgtctgc	forward amplicon primer
3184	Sip 1 dom 1 R	cagccttgatcccttgcaacc	reverse amplicon primer
3183	Sip 1 dom 1 F	gtcaacgtggagggcgag	forward amplicon primer
3182	SIP 1 dom 2 R	gocgggactgtcaactatgc	reverse amplicon primer
3181	SIP 1 dom 2 F	gaaggggaactcaggcctatg	forward amplicon primer
3180	Tip 1 R	ccaatgtgaanauccaggat	reverse amplicon primer
3179	Tip 1 F	aattcaacagctgctgctgngg	forward amplicon primer
3178	AIPC dom 1 F	gggcttggctttagtattgc	forward amplicon primer
3177	Mint 3 500 bp R	cagctggatctgtcttgatag	reverse amplicon primer
3176	Mint 3 500bp F	agctgtcacaggagcctat	forward amplicon primer
3175	Mint 1 dom2 R	cgcctgaggctgcagataatt	reverse amplicon primer
3174	Mint 1 dom2 F	ctaccagctcgttttcacgc	forward amplicon primer
3173	Mint 1 dom1 R	tctggcaggtggacagagg	reverse amplicon primer
3172	Mint 1 dom1 F	cggtgaccagatcatgtccat	forward amplicon primer
3171	PTN3 R	acgattgatcccccttcttc	reverse amplicon primer
3170	PTN3 F	agtcacctcgggacacctg	forward amplicon primer
3169	HTRA2 R	gggaagcttgggttcgaag	reverse amplicon primer
3168	HTRA2 F	ctgagtcaccagctccttgc	forward amplicon primer
3167	AIPC dom 1 R	ccccatctgtccacgaatg	reverse amplicon primer
3166	Mast 2 dom 1 F	actcttgccagcctctgg	forward amplicon primer
3165	Mupp1 dom 3 R	tgtgtctccaatgttgatcttc	reverse amplicon primer
3164	Mupp1 dom 3 F	acanaagcagtcgctgtga	forward amplicon primer
3163	Novel PDZ dom 1 R	cagcacctttacggcgctac	reverse amplicon primer
3162	Novel PDZ dom 1 F	aattgggtgagcctggaga	forward amplicon primer
3161	MAGI 2 dom 5 F	tgtggacatggagaaaggagc	forward amplicon primer
3160	Mast 1 dom 1 R	tgcacacaatgtgttggtgac	reverse amplicon primer
3159	Mast 1 dom 1 F	tgtctacatgggtgacacgga	forward amplicon primer
3158	Mast 2 dom 1 R	gtctgggtgatgatgatgg	reverse amplicon primer
3157	NSP dom 1 R	toctgagatcaogtctggaa	reverse amplicon primer
3156	NSP dom 1 F	aagccaaagagctgaaggacc	forward amplicon primer
3155	Elfin 1 dom 1 R	ccttgcttcacagagtgacc	reverse amplicon primer
3154	Elfin 1 dom 1 F	aagggaacttcaggaagcctct	forward amplicon primer

AVC		
No	Oligo Name	Sequence
		Description
3153	EBP50 dom 2 R	tcaactgacggatgaactg reverse amplicon primer
3152	EBP50 dom 2 F	caacctgcacagcagcaagt forward amplicon primer
3151	ZO 1 dom 2 R	gcttgccaactgaagacat reverse amplicon primer
3150	ZO 1 dom 2 F	acactgtgtaaatccggaa forward amplicon primer
3149	BBP50 dom 1 R	tgactggcccaactggc reverse amplicon primer
3148	BBP50 dom 1 F	agaagggtgcgaacggctac forward amplicon primer
3147	APXL dom 1 R	cgttcctgtctataacctga reverse amplicon primer
3146	APXL1 dom 1 F	tgagatcgtcggcatcaatg forward amplicon primer
3145	Grip 2 dom 5 R	gcagttgtccaggcgata reverse amplicon primer
3144	Grip 2 dom 5 F	gagccaggcgcaacagctact forward amplicon primer
3143	KIA0382 dom 1 R	atggctgtccatctctttg reverse amplicon primer
3142	KIA0382 dom 1 F	cggtcagtggagcaatoca forward amplicon primer
3141	Brbin dom 1 R	acaccacctgatgtcaaatoca reverse amplicon primer
3140	Brbin dom 1 F	agtgagggtgaanaaggaloca forward amplicon primer
3139	KIA0316 dom 1 R	tgaccaagatcgatgaacog reverse amplicon primer
3138	KIA0316 dom 1 F	aatgatgaacgggtcagcg forward amplicon primer
3137	KIA0751(RIM2) dom 1 R	aaagccgaacctgattcagta reverse amplicon primer
3136	KIA0751(RIM2) dom 1 F	caatgcttggtgagggttg forward amplicon primer
3135	Lim Mystique dom 1R	cogttgatggccaagattat reverse amplicon primer
3134	Lim Mystique dom 1F	agccaaggagagctgaccto forward amplicon primer
3133	Lim Protein dom 1 R	ccttgccgcatctttttaga reverse amplicon primer
3132	Lim Protein dom 1 F	cggtaaggattcaacatgoc forward amplicon primer
3131	MAGI 2 dom 5 R	cctccacgaatgctgaatoc reverse amplicon primer
3116	AIPC As (reverse)	gctgatccattgggaagutg Amplicon primer for real-time PCR
3115	AIPC S (forward)	gcattgtggacagatggg Amplicon primer for real-time PCR
3114	HER 1 As (reverse)	caggatccgtgatggtct PCR
3113	HRR 1 S (forward)	cgtttggaggttgatgacc Amplicon primer for real-time PCR
3112	HER 2 As (reverse)	ccacttgatggcacccttg PCR
3111	HER 2 S (forward)	tgtggacattgacgagacag Amplicon primer for real-time PCR

AVC		
No	Oligo Name	Sequence
		Description
		PCR
3110	FGFR3C AS (reverse)	cacgtccagctgtacgtct
		Amplicon primer for real-time
		PCR
3109	FGFR3C S (forward)	ctcgtctgttgagacaagtt
		Amplicon primer for real-time
		PCR
3108	b-Catenin AS (reverse)	gctgggtatctgatgtgca
		Amplicon primer for real-time
		PCR
3107	b-Catenin S (Forward)	gggtgcattccaagactag
		Amplicon primer for real-time
		PCR
3106	MUC-1 AS (reverse)	tgtccagctgccctagttc
		Amplicon primer for real-time
		PCR
3105	MUC-1 S (forward)	ttagcttgctgtctgtag
3414	RIM2 P7R	tgtgtgtcagggttgactctagaa
3413	RIM2 P7T	cacatttgaggagtgtaaacatcat
3412	RIM2 P6R	tggctccttgacagtagcttcc
3411	RIM2 P6F	gaccagggtgatgaagattagaatgg
3410	RIM2 P5R	ccaccaagttacatcttctt
3409	RIM2 P5F	gtgggactctaaaccaggctctg
3408	RIM2 P4R	tggccaccaagtaactcatttc
3407	RIM2 P4F	ctctaaccaccaggctgagagacaaa
3406	RIM2 P3R	tgtgttccatttggtgtcca
3405	RIM2 P3F	ttccagacagaagtgtataaaacaagag
3404	RIM2 P2R	tgcattgttcagtggtgtcca
3403	RIM2 P2F	ccaccaaatctctacaanaatgagott
3402	RIM2 P1R	tccagatcagcattgtccaa
3393	RIM2 P1F	acggcatgagagaagggaatag

Results: Table 6 shows the RNA expression in four cell lines as described utilizing the primers listed in Table 5. The results indicate that several of the target PDZ mRNAs are expressed in the selected cancer cell lines and are potential targets for therapeutic intervention. In the case of RIM2, alternatively spliced genes were observed; however, the primer sets indicate that the PDZ domain is expressed in these cell lines.

In Table 6, "+" is indicative of expression, and "-" is indicative of low or no expression. * - denotes that different primer pairs were used, corresponding to the pairs listed at the bottom of Table 5. For example, RIM2 P1 was evaluating RNA expression using RIM2 P1F (forward) and RIM2 P1R (reverse) primers.

5

Table 6
RNA expression in cell lines

	HCT116	HCT116 MUC1	MCF-7	ZR-75
BETA-CATENIN	+	+	+	+
FGFR3IIIc	+	+	+	+
HER1	+	+	+	+
HER2	+	+	+	+
MUC1	-	+	+	+
AIPC d1	-	-	-	+
APXL d1	+	+	+	+
DLG1 d1	+	+	+	+
DLG1 d2	+	+	+	+
EBP50 d1	+	+	+	+
EBP50 d2	+	+	+	+
ELFIN d1	+	+	+	+
ERBIN d1	+	+	+	+
GRIP2 d5	-	-	-	-
HTRA2 d1	+	+	+	+
INADL d3	+	+	+	+
KIA0316 d1	-	-	-	-
KIA0340 d1	-	-	-	-
KIA0382 d1	+	+	+	+
KIA0751 d1*	-	-	-	+
KIA1526 d1	-	-	-	-
LIM MYSTIQUE d1	+	+	+	+
LIM PROTEIN d1	+	+	+	+
MAGI2 d5	-	-	+	+
MAGI3 d5	+	+	+	+

	HCT116	HCT116 MUC1	MCF-7	ZR-75
MAST1 d1	-	-	-	-
MAST2 d1	+	+	-	+
MAST3 d1	+	+	+	+
MINT1 d1	-	-	-	+
MINT1 d2	-	-	-	-
MINT3 full-length	-	-	-	-
MUPP1 d3	-	-	+	+
MUPP1 d6	-	-	+	+
NOVEL PDZ d1	-	-	-	-
NSP d1	-	-	-	-
PAR3 d3	+	+	+	+
PICK1 d1	+	+	+	+
pIL-16 d1	-	-	-	+
PIN3 d1	+	+	+	+
PTPL1 d4	+	+	+	+
RGS3 d1	+	+	+	+
SIP1 d1	+	+	+	+
SIP1 d2	+	+	+	+
SITAC18 d1	-	-	-	-
SYNTROPHINy d1	-	-	-	-
TIP1 d1	+	+	+	+
VARTUL d4	+	+	+	+
ZO-1 d2	+	+	+	+
RIM2 P1*	+	+	+	+
RIM2 P2*	+	+	+	+
RIM2 P3*	+/-	+/-	+	+
RIM2 P4*	+	+	+	+
RIM2 P5*	+	+	+	+
RIM2 P6*	+	+	+	+
RIM2 P7*	+	+	+	+

Example 9: Knockdown of MUC1 Binding PDZ Proteins in Cancer Cells

The effects of knocking-down the PDZ domain proteins ZO-1, SIP1, LIM Mystique and KIAA0751 by siRNAs on anti-apoptotic function of MUC1 were examined in human non-small cell lung cancer A549 cells that endogenously express MUC1 and transfected human colon cancer HCT116 cells that exogenously express MUC1.

Cell culture and transfection: Human colon cancer HCT116 cells and human non-small lung cancer A549 were grown in Dulbecco's modified Eagle's medium (DMEM) and RPMI1640 medium, respectively, in a humidified 5% CO₂ atmosphere at 37°C. Media were supplemented with 10% fetal bovine serum (FBS), 100 units/ml of penicillin and 100 µg/ml of streptomycin. HCT116 cells were transfected with pIRES-puro2 or pIRES-puro2-MUC1 as described (Li *et al.*, 2001(a)) and stable transfectants were selected in the presence of 0.4 µg/ml puromycin (Calbiochem-Novabiochem).

Generation of siRNA for transfection: siRNAs were synthesized to knock-down expression of LIM-M (GI: 28866956), KIAA0751 (GI: 3882222), ZO-1 (GI: 28416399) and SIP1 (GI: 2047327) (Dharmacon, Inc.). The targeted sequences for these genes were as follows:

LIM Mystique: 5'-AAGCTGGTGAGACAACCTCTG-3'

KIAA0751: 5'-AACACCAAGGCTGAGAGACAA-3'

ZO-1: 5'-AAGTTGGCAACCAGATGTGGA-3'

SIP1: 5'-AAGCTGGCAAGAAGGATGTCA-3'

A nonspecific scrambled control siRNA (SCRsiRNA) was also synthesized (targeted sequence: 5'-AAGCGCGCTTTGTAGGATTCG-3') (Dharmacon, Inc.). Cells were plated, grown in antibiotic-free medium overnight, and then transiently transfected with siRNAs (0.2 – 20 nM) using Oligofectamine reagent (Invitrogen Life Technology, Inc.) and Opti-MEM 1 reduced serum medium (Invitrogen Life Technology, Inc.) according to the manufacturer's instructions.

Apoptosis assay: At 48 hr after siRNA transfection, cells were treated with 0, 10 or 100 µM cisplatin (CDDP, Sigma) for 24 hr to induce apoptosis. Apoptotic cells were quantified by analysis of sub-G1 DNA content. Cells were harvested, washed, with PBS, fixed with 75% ethanol, and incubated in PBS containing 200 µg/ml RNase A (Qiagen) for 15 min at 37°C. Cells were then stained with 50 µg/ml propidium iodide (Boehringer Mannheim) for 30 min at room temperature in the dark. DNA content was analyzed by flow cytometry (EPICS XL-MCL, Coulter Corp.).

Immunoblotting: Cells were incubated for the indicated times, harvested, washed with ice-cold PBS, and lysed in lysis buffer [150 mM NaCl, 50 mM Tris (pH 7.6), 5 mM EDTA, 0.5% NP-40, and protease inhibitor cocktail (Complete, Roche Diagnostics Corp)]. Whole cell lysates were subjected to SDS-PAGE, transferred to nitrocellulose membrane, and immunoblotted with antibodies against KIAA0751 (Rim2, Santa Cruz Biotechnology), SIP1 (NHERF2, Alpha Diagnostic International), ZO-1 (Zymed Laboratories) or β -actin (Clone AC-15; Sigma). The blots were developed by using the ECL kit (Amersham Pharmacia Biotech).

Results: In that MUC1 functions as anti-apoptotic protein, HCT116/vector cells were sensitive to apoptosis induced by CDDP (100 μ M) while HCT116/MUC1 cells were relatively resistant to apoptosis. Transient transfections of HCT116/MUC1 cells with KIAA0751siRNA and LIM-MsiRNA were associated with increased apoptotic responses to CDDP (FIG. 5). Similar results were obtained with A549 cells that endogenously express MUC1 (FIG. 5). The apoptosis-sensitizing effect of KIAA0751siRNA was significantly greater than that of LIM-MsiRNA in HCT116/MUC1 cells. Importantly, KIAA0751siRNA did not sensitize cells to apoptosis in MUC1-negative HCT116/vector cells at either 10 μ M or 100 μ M CDDP, indicating that the observed apoptosis-sensitizing effect of KIAA0751siRNA is dependent on MUC1 (FIG. 6) and that the KIAA0751 protein is involved in the anti-apoptotic function of MUC1. Conversely, neither SIP1siRNA nor ZO1siRNA significantly affected CDDP-induced apoptosis in A549 and HCT116/MUC1 cells (FIG. 7 and FIG. 8).

The knock-down effects of siRNAs on ZO-1, KIAA0751 and SIP1 were determined by immunoblotting and these proteins were knocked-down by approximately 50-70%.

Example 10: Comparative Binding of MUC1 Carboxy-terminal Isoforms

Using the modified ELISA described *supra* in Example 6, the effect of two variant carboxy-terminal MUC1 peptides were examined. Two MUC1 isoforms with an A/T substitutions at the fifth amino acid residue from the carboxy-terminal end have been reported in the literature, e.g., carboxy-terminal AAASANL disclosed in GenBank P15941 [gi:547937] and carboxy-terminal AATSANL disclosed in GenBank A35175 [gi:11385307]. Peptides were prepared consisting of the TAT sequence SEQ ID NO: 102 and the terminal nine amino acid residues of the relevant MUC1 sequence, i.e., YGRKKRRQRRRAVAATSANL (SEQ ID NO: 134) and YGRKKRRQRRRAVAASANL

(SEQ ID NO: 135) and titrated binding to RIM2 and ZO1 d2. As shown in FIG. 9, the two isoforms bind to RIM3 and ZO1 d2 with similar affinities.

Example 11: Comparative Binding of Ligands to PDZ Domains

Using the modified ELISA described *supra* in Example 6, RIM2, ZO1 d2, SIP1 d1 and Lim Mystique were titrated with three peptides consisting of 9 carboxy-terminal amino acid residues and TAT SEQ ID NO: 102, i.e., biotinylated peptides:

YGRKKRRQRRRARGDRKRIV (SEQ ID NO: 136);

YGRKKRRQRRRQDEEGIWA (SEQ ID NO: 137); and YGRKKRRQRRRAAATSINL (SEQ ID NO 138).

As shown in Table 7, SEQ ID NO: 137 binds most tightly to RIM2, followed by SEQ ID NO: 136 and SEQ ID NO: 138. All three peptides bind SIP1 and Lim Mystique with lower affinity than the MUC1 derived sequence SEQ ID NO: 96 (of Table 4, Example 7), while binding with greater affinity to RIM2 and ZO1 d2, indicating greater selectivity for the later two PDZ domains than the MUC1 derived sequence. SEQ ID NO: 137 binds RIM2 more strongly than ZO1 d2.

Table 7

EC₅₀ Values for PDZ Binding

Peptide	RIM2	ZO1 d2	SIP1	Lim Mys.
SEQ ID NO: 136	0.02 μ M	0.02 μ M	> 5 μ M	> 5 μ M
SEQ ID NO: 137	0.005 μ M	0.05 μ M	> 5 μ M	> 5 μ M
SEQ ID NO: 138	0.04 μ M	0.008 μ M	> 5 μ M	> 5 μ M

Example 12: Competitive Binding of Ligands to PDZ Domains

Using the modified ELISA described *supra* in Example 6, the ability of the peptides: YGRKKRRQRRRARGDRKRIV (SEQ ID NO: 136) (AVC 1796); YGRKKRRQRRRQDEEGIWA (SEQ ID NO: 137) (AVC 1790); and YGRKKRRQRRRAAATSINL (SEQ ID NO 138) (AVC 1791), to compete with the binding of the biotinylated TAT-MUC1 derived peptide YGRKKRRQRRRAAATSANL (SEQ ID NO: 134) to PDZ domains. FIG. 10 shows that SEQ ID NO: 136 (AVC 1796) is the best competitive inhibitor for biotinylated SEQ ID NO: 134 (TAT-MUC1) binding to RIM2, though SEQ ID NO: 137 (AVC 1790) has a lower EC₅₀ for binding to RIM2 (of Example 10). Similar experiments for binding to ZO1 d2 indicated that SEQ ID NO: 136 (AVC 1796) can

also compete for binding to ZO1 d2 while SEQ ID NO: 137 (AVC 1790) is only a relatively weak competitor for ZO1 d2. Self-competition experiments indicated that SEQ ID NO: 137 (AVC 1790) acts the most like a traditional competitive inhibitor of the three peptides tested.

Example 13: Matrix Profile of Inhibitors

5 The biotinylated peptides SEQ ID NO: 136 (AVC 1796), SEQ ID NO: 137 (AVC 1790), and SEQ ID NO: 138 (AVC 1791), were screened for binding to PDZ domains as described in Example 7. The results, shown in FIG. 11, 12 and 13, represent the absorbance and standard deviation of interactions of higher relative strength. The data in FIG. 13 for PDZK1, PTPL1 d5, MUPP1 d4 and INADL d1 have high standard deviations and thus
10 require further verification to validate intensity of binding.

Example 14: Identification of Inhibitors of the MUC1-RIM2 Interaction

Using the modified ELISA described *supra* in Example 7, the binding to the RIM2 PDZ domain of the biotinylated peptide sequences listed in Table 8 were examined. The biotinylated 20-mer amino acid peptides were added at varying concentrations (0.001 μ M to
15 10 μ M) to the plated GST-RIM2 PDZ domain. Relative EC₅₀ values were calculated from a curve fit of the data for each interaction.

Table 8
Peptide binding to PDZ domain 1 of RIM2

Peptide (designation)	Relative EC ₅₀	SEQ ID NO:
YGRKKRRQRRRAVAATSANL	0.065	SEQ ID NO: 134
YGRKKRRQRRRARGDRKRIV (AVC#1796)	0.02	SEQ ID NO: 136
YGRKKRRQRRRQDEBEGIWA (AVC#1790)	0.005	SEQ ID NO: 137
YGRKKRRQRRRAVAATSINL (AVC#1791)	0.04	SEQ ID NO: 138
YGRKKRRQRRRAVAATYSNL (AVC#1793)	0.6	SEQ ID NO: 139
YGRKKRRQRRRARGDRKRWA (AVC#1821)	0.007	SEQ ID NO: 140
YGRKKRRQRRRARGDRKRWL (AVC#1822)	0.008	SEQ ID NO: 141
YGRKKRRQRRRARSDRGIWA (AVC#1823)	<0.01	SEQ ID NO: 142
YGRKKRRQRRRAVAATGIWA	<0.01	SEQ ID NO: 143

Peptide (designation)	Relative EC50	SEQ ID NO:
(AVC#1827)		
YGRKKRRQRRRQDEEFTWA (AVC#1828)	0.24	SEQ ID NO: 144
YGRKKRRQRRRARSDRTTWA (AVC#1829)	<0.01	SEQ ID NO: 145
YGRKKRRQRRRARSDRTIIA (AVC#1830)	0.013	SEQ ID NO: 146
YGRKKRRQRRRARSDRKRIA (AVC#1831)	0.045	SEQ ID NO: 147
YGRKKRRQRRRSRTDRKYWA (AVC#1832)	<0.01	SEQ ID NO: 148
YGRKKRRQRRRQDEEBGIWS (AVC#1833)	0.05	SEQ ID NO: 149
YGRKKRRQRRRSRTVREIWA (AVC#1834)	<0.01	SEQ ID NO: 150
YGRKKRRQRRRSVTSTINL (AVC#1835)	0.09	SEQ ID NO: 151
YGRKKRRQRRRARGD RKIRV (AVC#1836)	0.01	SEQ ID NO: 152
YGRKKRRQRRRARTRDKVEV (AVC#1837)	0.04	SEQ ID NO: 153
YGRKKRRQRRRARGD RKYIV (AVC#1838)	0.013	SEQ ID NO: 154
YGRKKRRQRRRSRTDRKYQI (AVC#1839)	0.022	SEQ ID NO: 155
YGRKKRRQRRRARGDVRLML (AVC#1840)	~0.03	SEQ ID NO: 156
YGRKKRRQRRRARGD RKVPV (AVC#1841)	0.045	SEQ ID NO: 157
YGRKKRRQRRRQDERRLIVL (AVC#1842)	0.078	SEQ ID NO: 158
YGRKKRRQRRRARGDRLVSL (AVC#1843)	0.068	SEQ ID NO: 159
YGRKKRRQRRRARGTRLVWV (AVC#1844)	<0.01	SEQ ID NO: 160
YGRKKRRQRRRARGD RYRIV (AVC#1845)	0.038	SEQ ID NO: 161
YGRKKRRQRRRSRTDRLEYV (AVC#1846)	0.01	SEQ ID NO: 162
YGRKKRRQRRRARGDRLIV (AVC#1847)	0.132	SEQ ID NO: 163
YGRKKRRQRRRARGDRTIY (AVC#1848)	~0.03	SEQ ID NO: 164
YGRKKRRQRRRARGD RRRIV (AVC#1849)	0.037	SEQ ID NO: 165
YGRKKRRQRRRARGD RKKIV (AVC#1850)	0.047	SEQ ID NO: 166
YGRKKRRQRRRARSD RKIRV	0.047	SEQ ID NO: 167

Peptide (designation)	Relative EC50	SEQ ID NO:
(AVC#1851)		
YGRKKRRQRRRENKDKEYV	0.013	SEQ ID NO: 168
(AVC#1852)		
YGRKKRRQRRRGMTSSSSVV	0.135	SEQ ID NO: 169
(AVC#1853)		
YGRKKRRQRRRARGRRRETWV	<0.01	SEQ ID NO: 170
(AVC#1854)		
YGRKKRRQRRRQDERVETRV	0.88	SEQ ID NO: 171
(AVC#1855)		
YGRKKRRQRRRLQRRRETQV	0.033	
(AVC#1856)		

Example 15: Sensitization of Human Cancer Cells to Chemotherapeutic Agents by Inhibitor Peptides

- The effects of peptide inhibitors of the MUC1-RIM2 interaction on sensitizing
- MUC1-expressing human cancer cells to chemotherapeutic agents is investigated. Suitable human cancer cells include MUC1 transfected HCT116 cells (and vector control cells) and human non-small cell lung cancer A549 cells that endogenously express MUC1. HCT116 cells and A549 cells are grown in Dulbecco's modified Eagle's medium (DMEM) and RPMI1640 medium, respectively, in a humidified 5% CO₂ atmosphere at 37°C. Media is supplemented with 10% fetal bovine serum (FBS), 100 units/ml of penicillin and 100 µg/ml of streptomycin. HCT116 cells are transfected with pIRES-puro2 or pIRES-puro2-MUC1 as described (Li et al., 2001(a)) and stable transfectants are selected in the presence of 0.4 µg/ml puromycin (Calbiochem-Novabiochem).

- Cancer cells are incubated with inhibitor peptides comprising an internalizing peptide
- sequence, including SEQ ID NO: 108 or SEQ ID NO: 119, and an inhibitor sequence, including SEQ ID NO: 134 through SEQ ID NO: 171. Suitable controls are also run in parallel. Subsequently, cells are treated with 0, 10 or 100 µM cisplatin (CDDP, Sigma) for 24 hr to induce apoptosis. Apoptotic cells are quantified by analysis of sub-G1 DNA content. Cells are harvested, washed, with PBS, fixed with 75% ethanol, and incubated in PBS containing 200 µg/ml RNase A (Qiagen) for 15 min at 37°C. Cells were then stained with 50 µg/ml propidium iodide (Boehringer Mannheim) for 30 min at room temperature in the dark. DNA content was analyzed by flow cytometry (EPICS XL-MCL, Coulter Corp.).

Example 16: Human Cancer Cell in *In Vivo* Xenograft Models

The antitumor effect of inhibitor peptides, as described in Example 14, are assessed against MUC1-expressing human cancer cell xenograft tumor models. Suitable tumor cells include MUC1 transfected human colon cancer HCT116 cells (and vector control cells),

5 human breast cancer ZR-75 cells and human non-small cell lung cancer A549 cells. Human tumors are implanted subcutaneously into the flanks of nude mice. As the tumors reach a predetermined size of approximately 100 mm³, the mice are randomized into therapy groups. Inhibitor peptides and suitable controls are administered by IV injection or intraperitoneal injection for a suitable time period, e.g., 5 daily doses at suitable doses levels, e.g., maximum

10 tolerated dose (MTD), 1/2 MTD, 1/4 MTD, or other suitable dose if an MTD is not established. Mean tumor volumes are determined three times per week. Tumor volume is determined by caliper measurements (mm) and using the formula for an ellipsoid sphere: $L \times W^2/2 = \text{mm}^3$, where L is the length in mm and W is the width in mm. The formula is also used to calculate tumor weight (mg), assuming unit density (1 mm³ = 1 mg). The study is

15 terminated when the tumor volumes in the control group(s) reach approximately 2000 mm³. The time to reach evaluation size for the tumor of each animal is used to calculate the overall delay in the growth of the median tumor (T-C).

* * * * *

The present invention has been shown by both description and examples. The

20 Examples are only examples and cannot be construed to limit the scope of the invention. One of ordinary skill in the art will envision equivalents to the inventive process described by the following claims that are within the scope and spirit of the claimed invention.

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CLAIMS

1. A method of inhibiting the binding of the cytoplasmic domain of MUC1 to a PDZ domain, comprising contacting said PDZ domain with an effective amount of an agent that competes with the binding of the C-terminal region of said cytoplasmic domain of MUC1 with said PDZ domain.
2. The method of claim 1, wherein said PDZ domain is ZO-1 d2, SIP1 d1, LIM MYSTIQUE, AIPC, KIAA0751, MAST2, PRIL-16 d1, GRIP2 d5, SITAC 18, NSP or KIAA1526 d1.
3. The method of claim 1, wherein said agent that competes with binding of said C-terminal region of cytoplasmic domain of MUC1 with said PDZ domain is a peptide of the formula $X^1\text{-aa}^2\text{-aa}^1\text{-aa}^0$, wherein aa^0 is a hydrophobic aliphatic amino acid residue or a hydrophobic aromatic amino acid residue, aa^2 is a hydrophobic aliphatic amino acid residue, hydrophobic aromatic amino acid residue, polar amino acid residue, basic amino acid residue or an acidic amino acid residue, aa^1 is an amino acid residue and X^1 is a sequence of 0 to 50 amino acid residues.
4. The method of claim 3, wherein aa^0 is V, L, A, I, S or Y and aa^2 is V, L, A, I, F, Y, W, Q, N, S, T, R, K, D or E.
5. The method of claim 3, wherein $\text{aa}^2\text{-aa}^1\text{-aa}^0$ is a sequence selected from SEQ ID NO: 1 through SEQ ID NO: 40.
6. The method of claim 3, wherein the carboxy-terminus of said peptide of formula $X^1\text{-aa}^2\text{-aa}^1\text{-aa}^0$ comprises the carboxy-terminal 4, 5, 6, 7, 8 or 9 amino acid residues of a nine amino acid residue sequence selected from SEQ ID NO: 41 through SEQ ID NO: 94.
7. The method of claim 3, wherein the carboxy-terminus of said peptide of formula $X^1\text{-aa}^2\text{-aa}^1\text{-aa}^0$ comprises the carboxy-terminal 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 amino acid residues of SEQ ID NO: 95 or SEQ ID NO: 96.
8. The method of claim 3, wherein the amino terminus of X^1 comprises $X^2\text{-X}^3$, wherein X^2 is a transmembrane transporter peptide sequence and X^3 is an optional linker sequence.

9. The method of claim 8, wherein X^2 is a sequence selected from SEQ ID NO 97 through SEQ ID NO: 127.
10. The method of claim 9, wherein X^2 is SEQ ID NO: 102, SEQ ID NO: 108 or SEQ ID NO: 119.
11. A method of inhibiting the binding of the cytoplasmic domain of MUC1 to one or more PDZ proteins within a MUC1 expressing cancer cell comprising contacting said MUC1 expressing cancer cell with an effective amount of an agent that competes with the binding of the C-terminal region of said cytoplasmic domain of MUC1 with said PDZ protein.
12. The method of claim 11, wherein one or more PDZ proteins is/are selected from the group consisting of ZO-1 d2, SIP1 d1, LIM MYSTIQUE, AJPC, KIAA0751, MAST2, and PRIL-16 d1.
13. The method of claim 11, wherein said agent that competes with binding of said C-terminal region of cytoplasmic domain of MUC1 with said one or more PDZ proteins is a peptide of the formula $X^1\text{-aa}^2\text{-aa}^1\text{-aa}^0$, wherein aa^0 is a hydrophobic aliphatic amino acid residue, aa^2 is a hydrophobic aliphatic amino acid residue or a hydrophobic aromatic amino acid residue, hydrophobic aromatic amino acid residue, polar amino acid residue, basic amino acid residue or an acidic amino acid residue, aa^1 is an amino acid residue and X^1 is a sequence of 0 to 50 amino acid residues.
14. The method of claim 13, wherein aa^0 is V, L, A, I, S or Y and aa^2 is V, L, A, I, F, Y, W, Q, N, S, T, R, K, D or E.
15. The method of claim 13, wherein $\text{aa}^2\text{-aa}^1\text{-aa}^0$ is a sequence selected from SEQ ID NO: 1 through SEQ ID NO: 40.
16. The method of claim 13, wherein the carboxy-terminus of said peptide of formula $X^1\text{-aa}^2\text{-aa}^1\text{-aa}^0$ comprises the carboxy-terminal 4, 5, 6, 7, 8 or 9 amino acid residues of a nine amino acid residue sequence selected from SEQ ID NO: 41 through SEQ ID NO: 94.
17. The method of claim 13, wherein the carboxy-terminus of said peptide of formula $X^1\text{-aa}^2\text{-aa}^1\text{-aa}^0$ comprises the carboxy-terminal 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 amino acid residues of SEQ ID NO: 95 or SEQ ID NO: 96.

18. The method of claim 13, wherein the amino terminus of X^1 comprises X^2 - X^3 , wherein X^2 is a transmembrane transporter peptide sequence and X^3 is an optional linker sequence.
19. The method of claim 18, wherein X^2 is a sequence selected from SEQ ID NO: 97 through SEQ ID NO: 127.
- 5 20. The method of claim 19, wherein X^2 is SEQ ID NO: 102, SEQ ID NO: 108 or SEQ ID NO: 119.
21. A method of enhancing the sensitivity of MUC1-expressing cancer cells to chemotherapeutic agents comprising contacting said MUC1-expressing cancer with an effective amount of a peptide of the formula X^1 - aa^2 - aa^1 - aa^0 , wherein aa^0 is a hydrophobic
10 aliphatic amino acid residue or a hydrophobic aromatic amino acid residue, aa^2 is a hydrophobic aliphatic amino acid residue, hydrophobic aromatic amino acid residue, polar amino acid residue, basic amino acid residue or an acidic amino acid residue, aa^1 is an amino acid residue and X^1 is a sequence of 0 to 50 amino acid residues.
22. The method of claim 21, wherein aa^0 is V, L, A, I, S or Y and aa^2 is V, L, A, I, F, Y,
15 W, Q, N, S, T, R, K, D or E.
23. The method of claim 21, wherein aa^2 - aa^1 - aa^0 is a sequence selected from SEQ ID NO: 1 through SEQ ID NO: 40.
24. The method of claim 21, wherein the carboxy-terminus of said peptide of formula X^1 - aa^2 - aa^1 - aa^0 comprises the carboxy-terminal 4, 5, 6, 7, 8 or 9 amino acid residues of a nine
20 amino acid residue sequence selected from SEQ ID NO: 41 through SEQ ID NO: 94.
25. The method of claim 21, wherein the carboxy-terminus of said peptide of formula X^1 - aa^2 - aa^1 - aa^0 comprises the carboxy-terminal 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 amino acid residues of SEQ ID NO: 95 or SEQ ID NO: 96.
26. The method of claim 21, wherein the amino terminus of X^1 comprises X^2 - X^3 , wherein
25 X^2 is a transmembrane transporter peptide sequence and X^3 is an optional linker sequence.
27. The method of claim 26, wherein X^2 is a sequence selected from SEQ ID NO: 97 through SEQ ID NO: 127.

28. The method of claim 27, wherein X^2 is SEQ ID NO: 102, SEQ ID NO: 108 or SEQ ID NO: 119.
29. A method of killing MUC1-expressing cancer cells comprising contacting said MUC1-expressing cancer cells with an effective amount of a chemotherapeutic agent and an effective amount of a peptide of the formula X^1 -aa²-aa¹-aa⁰, wherein aa⁰ is a hydrophobic aliphatic amino acid residue or a hydrophobic aromatic amino acid residue, aa² is a hydrophobic aliphatic amino acid residue, hydrophobic aromatic amino acid residue, polar amino acid residue, basic amino acid residue or an acidic amino acid residue, aa¹ is an amino acid residue and X^1 is a sequence of 0 to 50 amino acid residues.
30. The method of claim 29, wherein said chemotherapeutic agent is a DNA-interactive agent, a tubulin interactive agent, and an antimetabolite chemotherapeutic agent.
31. The method of claim 29, wherein aa⁰ is V, L, A, I, S or Y and aa² is V, L, A, I, F, Y, W, Q, N, S, T, R, K, D or E.
32. The method of claim 29, wherein aa²-aa¹-aa⁰ is a sequence selected from SEQ ID NO: 1 through SEQ ID NO: 40.
33. The method of claim 29, wherein the carboxy-terminus of said peptide of formula X^1 -aa²-aa¹-aa⁰ comprises the carboxy-terminal 4, 5, 6, 7, 8 or 9 amino acid residues of a nine amino acid residue sequence selected from SEQ ID NO: 41 through SEQ ID NO: 94.
34. The method of claim 29, wherein the carboxy-terminus of said peptide of formula X^1 -aa²-aa¹-aa⁰ comprises the carboxy-terminal 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 amino acid residues of SEQ ID NO: 95 or SEQ ID NO: 96.
35. The method of claim 29, wherein the amino terminus of X^1 comprises X^2 - X^3 , wherein X^2 is a transmembrane transporter peptide sequence and X^3 is an optional linker sequence.
36. The method of claim 35, wherein X^2 is a sequence selected from SEQ ID NO: 97 through SEQ ID NO: 127.
37. The method of claim 36, wherein X^2 is SEQ ID NO: 98, SEQ ID NO: 104 or SEQ ID NO: 119.

38. A method of killing MUC1-expressing cancer cells comprising contacting said MUC1-expressing cancer cells with an effective amount of a chemotherapeutic agent and an effective amount of an agent that inhibits the binding of the carboxy-terminal of the cytoplasmic tail of MUC1 with the PDZ domain of KIAA0751.
- 5 39. The method of claim 38, wherein said chemotherapeutic agent is a DNA-interactive agent, a tubulin interactive agent, and an antimetabolite chemotherapeutic agent.
40. The method of claim 38, wherein said agent that inhibits the binding of the carboxy-terminal of the cytoplasmic tail of MUC1 with the PDZ domain of KIAA0751 is a peptide of the formula $X^1\text{-aa}^2\text{-aa}^1\text{-aa}^0$, wherein aa^0 is a hydrophobic aliphatic amino acid residue or a
- 10 hydrophobic aromatic acid residue, aa^2 is a hydrophobic aliphatic amino acid residue, hydrophobic aromatic amino acid residue, polar amino acid residue, basic amino acid residue or an acidic amino acid residue, aa^1 is an amino acid residue and X^1 is a sequence of 0 to 50 amino acid residues.
41. The method of claim 40, wherein aa^0 is V, L, A, I, S or Y and aa^2 is V, L, A, I, F, Y, W, Q, N, S, T, R, K, D or E.
- 15 42. The method of claim 40, wherein $\text{aa}^2\text{-aa}^1\text{-aa}^0$ is a sequence selected from SEQ ID NO: 1 through SEQ ID NO: 40.
43. The method of claim 40, wherein the carboxy-terminus of said peptide of formula $X^1\text{-aa}^2\text{-aa}^1\text{-aa}^0$ comprises the carboxy-terminal 4, 5, 6, 7, 8 or 9 amino acid residues of a nine
- 20 amino acid residue sequence selected from SEQ ID NO: 41 through SEQ ID NO: 94.
44. The method of claim 40, wherein the carboxy-terminus of said peptide of formula $X^1\text{-aa}^2\text{-aa}^1\text{-aa}^0$ comprises the carboxy-terminal 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 amino acid residues of SEQ ID NO: 95 or SEQ ID NO: 96.
45. The method of claim 40, wherein the amino terminus of X^1 comprises $X^2\text{-X}^3$, wherein
- 25 X^2 is a transmembrane transporter peptide sequence and X^3 is an optional linker sequence.
46. The method of claim 45, wherein X^2 is a sequence selected from SEQ ID NO: 97 through SEQ ID NO: 127.

47. The method of claim 45, wherein X^2 is SEQ ID NO: 102, SEQ ID NO: 108 or SEQ ID NO: 119.

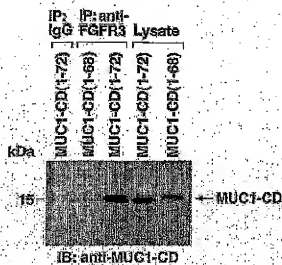


FIG. 1

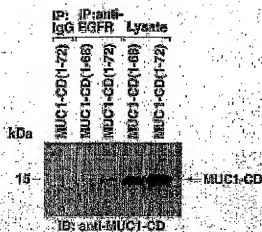
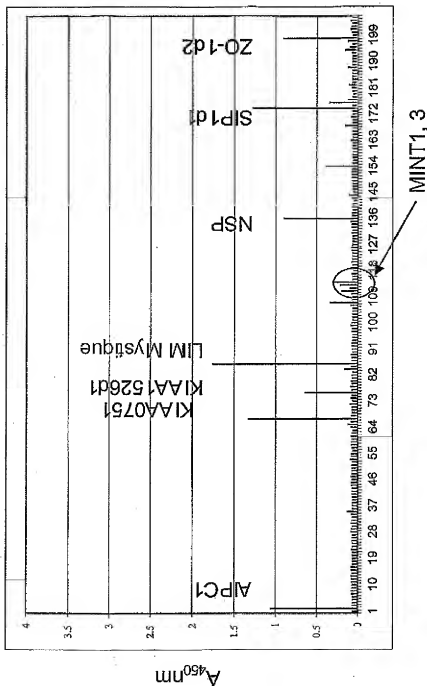
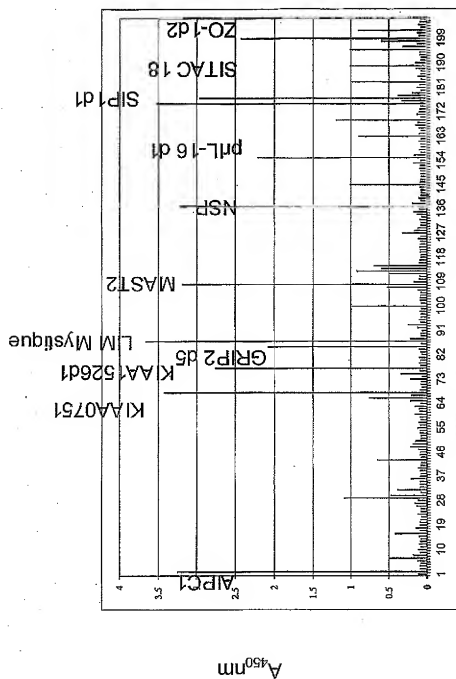


FIG. 2



Binding of 0.01 uM MUC1 C-terminus to PDZ domains

FIG. 3



Binding of 0.1 uM MUC1 C-terminus to PDZ domains

FIG. 4

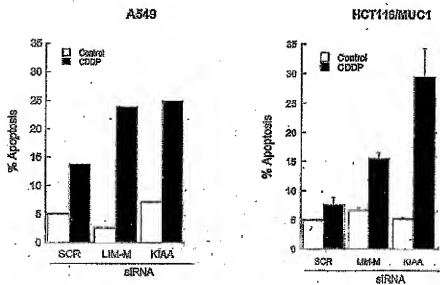


FIG. 5

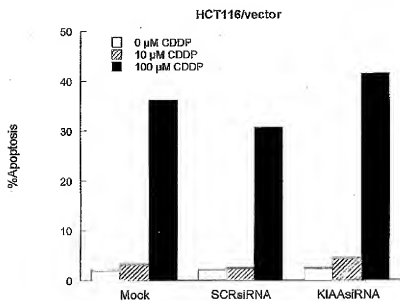


FIG. 6

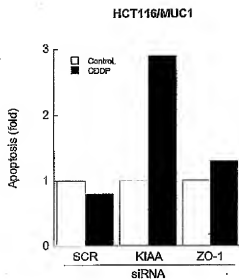


FIG. 7

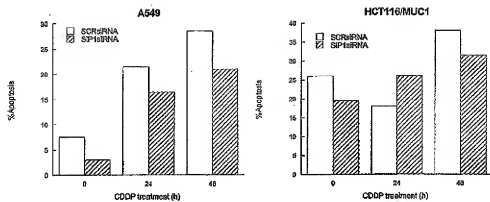


FIG. 8

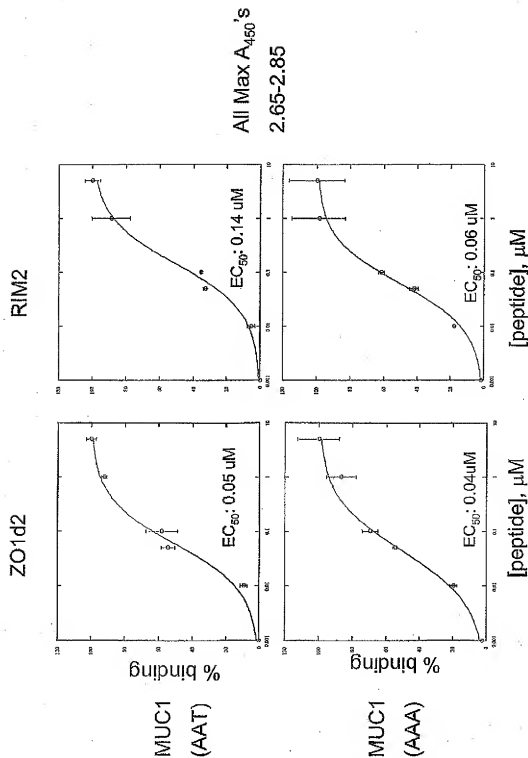


FIG. 9

Itak-MUC1e1 μ M, PDZ-REM2

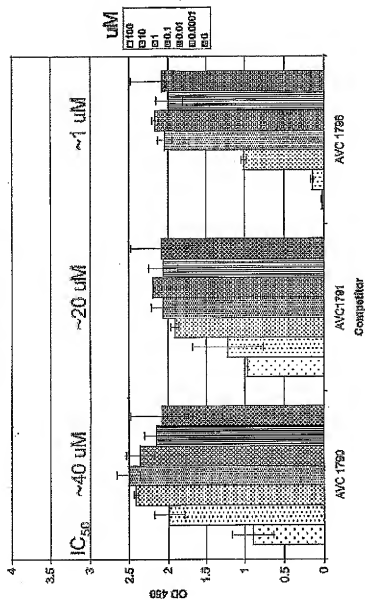
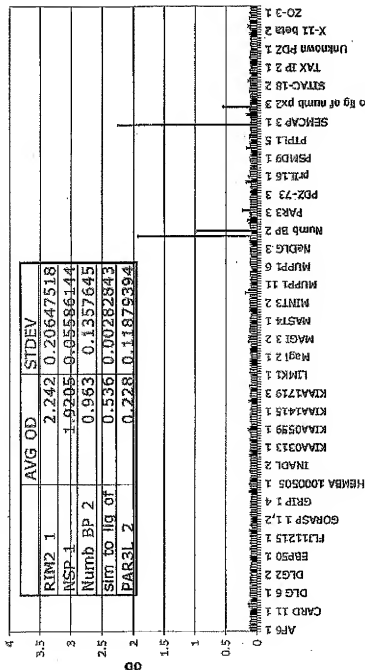


FIG. 10

SEQ ID NO: 137 (AVC 1790) = 0.01 μ M

PDZ

FIG. 11

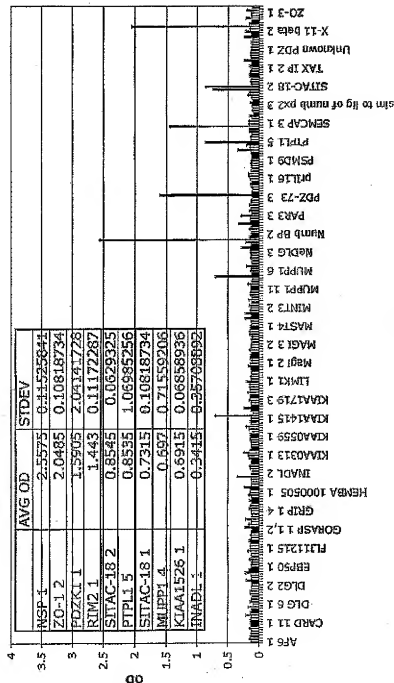
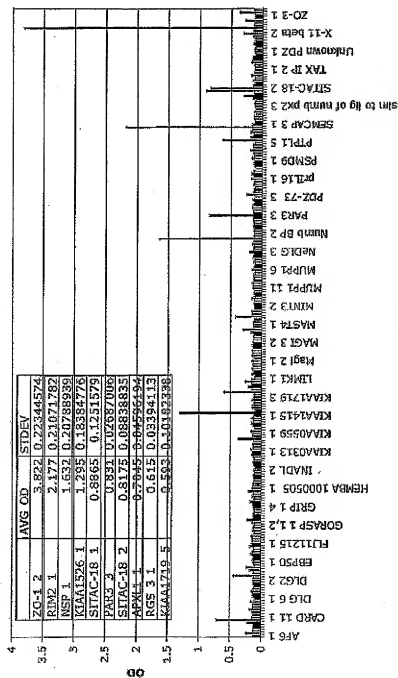
SEQ IS NO: 136 (AVC 1796) - 0.025 μ M

FIG. 12

SEQ ID NO: 138 (AVC1791) = 0.05 μ MPDZ
FIG. 13

SEQUENCE LISTING

<110> BELMARES, MICHAEL P.
LU, PETER S.
GARMAN, JONATHAN DAVID
JECMINIK, ALBERT A.
KHARANDA, SURENDER
AGATA, NAOKI
KUFFE, DONALD W.

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<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 57

Asp Ser Ser Arg Lys Glu Tyr Phe Ile
1 5

<210> 58
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<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 58

Lys Asn Lys Asp Lys Glu Tyr Tyr Val
1 5

<210> 59
<211> 9
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<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 59

Val Thr Asp His Lys Thr Glu Leu Val
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<210> 60

<211> 9

<212> PRT

<213> Artificial Sequence

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<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

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Gln Asp Glu Glu Glu Gly Ile Trp Ala
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<210> 61

<211> 9

<212> PRT

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<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 61

Ala Val Ala Ala Thr Ser Ile Asn Leu
1 5

<210> 62

<211> 9

<212> PRT

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<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 62

Ala Val Ala Ala Thr Tyr Ser Asn Leu
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<210> 63

<211> 9

<212> PRT

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<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 63

Ala Arg Gly Asp Arg Lys Arg Trp Ala

1 . 5

<210> 64
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Ala Arg Gly Asp Arg Lys Arg Trp Leu
1 5

<210> 65
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<400> 65

Ala Val Ala Ala Thr Gly Ile Trp Ala
1 5

<210> 66
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<400> 66

Gln Asp Glu Glu Glu Thr Ile Trp Ala
1 5

<210> 67
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Ala Arg Ser Asp Arg Thr Ile Trp Ala
1 5

<210> 68
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<212> PRT
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<400> 68

Ala Arg Ser Asp Arg Thr Ile Ile Ala
1 5

<210> 69
<211> 9
<212> PRT
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<400> 69

Ala Arg Ser Asp Arg Lys Arg Ile Ala
1 5

<210> 70
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<400> 70

Ser Arg Thr Asp Arg Lys Tyr Trp Ala
1 5

<210> 71
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<400> 71

Gln Asp Glu Glu Gly Ile Trp Ser
1 5

<210> 72
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Ser Arg Thr Val Arg Glu Ile Trp Ala
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<210> 73

<211> 9

<212> PRT

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Ser Val Thr Ser Thr Ser Ile Asn Leu
1 5

<210> 74

<211> 9

<212> PRT

<213> Artificial Sequence

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<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 74

Ala Arg Gly Asp Arg Lys Ile Arg Val
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<210> 75

<211> 9

<212> PRT

<213> Artificial Sequence

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<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 75

Ala Arg Thr Asp Arg Lys Val Glu Val
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<210> 76

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 76

Ala Arg Gly Asp Arg Lys Tyr Ile Val
1 5

<210> 77
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<400> 77

Ser Arg Thr Asp Arg Lys Tyr Gln Ile
1 5

<210> 78
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<400> 78

Ala Arg Gly Asp Val Arg Leu Met Leu
1 5

<210> 79
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<400> 79

Ala Arg Gly Asp Arg Lys Val Pro Val
1 5

<210> 80
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<400> 80

Gln Asp Glu Arg Arg Leu Ile Val Leu
1 5

<210> 81
<211> 9
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<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 81

Ala Arg Gly Asp Arg Leu Val Ser Leu
1 5

<210> 82

<211> 9

<212> PRT

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<400> 82

Ala Arg Gly Thr Arg Leu Val Trp Val
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<210> 83

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 83

Ala Arg Gly Asp Arg Tyr Arg Ile Val
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<210> 84

<211> 9

<212> PRT

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<220>

<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 84

Ser Arg Thr Asp Arg Leu Glu Tyr Val
1 5

<210> 85

<211> 9

<212> PRT

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<400> 85

Ala Arg Gly Asp Arg Leu Glu Ile Val
1 5

<210> 86

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 86

Ala Arg Gly Asp Arg Thr Ile Ile Tyr
1 5

<210> 87

<211> 9

<212> PRT

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<220>

<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 87

Ala Arg Gly Asp Arg Arg Arg Ile Val
1 5

<210> 88

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 88

Ala Arg Gly Asp Arg Lys Lys Ile Val
1 5

<210> 89

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 89

Ala Arg Ser Asp Arg Lys Arg Ile Val
1 5

<210> 90
<211> 9
<212> PRT
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<220>
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<400> 90

Lys Asn Lys Asp Lys Glu Tyr Tyr Val
1 5

<210> 91
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
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<400> 91

Gly Met Thr Ser Ser Ser Ser Val Val
1 5

<210> 92
<211> 9
<212> PRT
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<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE
<400> 92

Ala Arg Gly Arg Arg Glu Thr Trp Val
1 5

<210> 93
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE
<400> 93

Gln Asp Glu Arg Val Glu Thr Arg Val
1 5

<210> 94
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
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<400> 94

Leu Gln Arg Arg Arg Gln Thr Gln Val
 1 5

<210> 95
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 95

Asn Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala Val Ala Ala Ala
 1 5 10 15

Ser Ala Asn Leu
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<210> 96
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 96

Asn Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala Val Ala Ala Thr
 1 5 10 15

Ser Ala Asn Leu
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<210> 97
 <211> 16
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 97

Arg Gln Ile Lys Ile Trp Phe Gln Asn Arg Arg Met Lys Trp Lys Lys
 1 5 10 15

<210> 98

<211> 19
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 98

Ser Gly Arg Gln Ile Lys Ile Trp Phe Gln Asn Arg Arg Met Lys Trp
 1 5 10 15

Lys Lys Cys

<210> 99
 <211> 16
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 99

Arg Arg Trp Arg Arg Trp Trp Arg Arg Trp Trp Arg Arg Trp Arg Arg
 1 5 10 15

<210> 100
 <211> 16
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 100

Lys Lys Trp Lys Met Arg Arg Asn Gln Phe Trp Ile Lys Ile Gln Arg
 1 5 10 15

<210> 101
 <211> 16
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 101

Lys Lys Trp Lys Met Arg Arg Asn Gln Phe Trp Ile Lys Ile Gln Arg
 1 5 10 15

<210> 102
 <211> 11

<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 102

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg
1 5 10

<210> 103
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 103

Gly Arg Arg Lys Arg Arg Gln Arg Arg Pro Pro Gln
1 5 10

<210> 104
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 104

Ser Gly Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Cys
1 5 10

<210> 105
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
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<400> 105

Arg Arg Arg Gln Arg Arg Lys Lys Arg Gly Tyr
1 5 10

<210> 106
<211> 11
<212> PRT
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<220>
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<400> 106

Tyr Ala Arg Ala Ala Arg Gln Ala Arg Ala
1 5 10

<210> 107

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 107

Arg Lys Lys Arg Arg Gln Arg Arg Arg
1 5

<210> 108

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 108

Arg Arg Arg Arg Arg Arg Arg Arg
1 5

<210> 109

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 109

Arg Arg Arg Arg Arg Arg
1 5

<210> 110

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 110

Arg Arg Arg Arg Arg Arg Arg Arg
1 5

<210> 111
<211> 6
<212> PRT
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<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 111

Arg Arg Arg Gln Arg Arg
1 5

<210> 112
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 112

Gly Trp Thr Leu Asn Ser Ala Gly Tyr Leu Leu Gly Lys Ile Asn Leu
1 5 10 15

Lys Ala Leu Ala Ala Leu Ala Lys Lys Ile Leu
20 25

<210> 113
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 113

Ala Gly Tyr Leu Leu Gly Lys Ile Asn Leu Lys Ala Leu Ala Ala Leu
1 5 10 15

Ala Lys Lys Ile Leu
20

<210> 114
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 114

Asp Ala Ala Thr Ala Thr Arg Gly Arg Ser Ala Ala Ser Arg Pro Thr
 1 5 10 15

Glu Arg Pro Arg Ala Pro Ala Arg Ser Ala Ser Arg Pro Arg Val
 20 25 30

Glu

<210> 115
 <211> 27
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE
 <400> 115

Gly Ala Leu Phe Leu Gly Phe Leu Gly Ala Ala Gly Ser Thr Met Gly
 1 5 10 15

Ala Trp Ser Gln Pro Lys Ser Lys Arg Lys Val
 20 25

<210> 116
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE
 <400> 116

Arg Gly Gly Arg Leu Ser Tyr Ser Arg Arg Arg Phe Ser Thr Ser Thr
 1 5 10 15

Gly Arg

<210> 117
 <211> 16
 <212> PRT
 <213> Artificial Sequence

<220>
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 <400> 117

Val Thr Val Val Leu Ala Leu Gly Ala Leu Ala Gly Val Gly Val Gly
 1 5 10 15

<210> 118
 <211> 16
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 118

Ala Ala Val Ala Leu Leu Pro Ala Val Leu Leu Ala Leu Ala Pro
 1 5 10 15

<210> 119
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 119

Leu Leu Ala Leu Lys Leu Ala Leu Lys Ala Leu Lys Ala Ala Leu Lys
 1 5 10 15

Leu Ala

<210> 120
 <211> 15
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 120

Arg Arg Arg Arg Asn Arg Thr Arg Arg Asn Arg Arg Arg Val Arg
 1 5 10 15

<210> 121
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 121

Pro Ile Arg Arg Arg Lys Lys Leu Arg Arg Leu Lys
 1 5 10

<210> 122
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 122

Arg Arg Gln Arg Arg Thr Ser Lys Leu Met Lys Arg
 1 5 10

<210> 123
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 123

Leu Leu Ile Ile Leu Arg Arg Arg Ile Arg Lys Gln Ala His Ala His
 1 5 10 15

Ser Lys

<210> 124
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 124

Pro Lys Lys Lys Arg Lys Val
 1 5

<210> 125
 <211> 16
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 125

Lys Arg Pro Ala Ala Ile Lys Lys Ala Gly Gln Ala Lys Lys Lys Lys
 1 5 10 15

<210> 126
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 126

Cys Met His Ile Glu Ser Leu Asp Ser Tyr Thr Cys
1 5 10

<210> 127
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 127

Cys Met Tyr Ile Glu Ala Leu Asp Lys Tyr Ala Cys
1 5 10

<210> 128
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 128

Gly Gly Gly Gly Ser
1 5

<210> 129
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 129

Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Val Asp
1 5 10

<210> 130
<211> 18
<212> PRT
<213> Artificial Sequence

<220>

<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 130

Lys Glu Ser Gly Ser Val Ser Ser Glu Gln Leu Ala Gln Phe Arg Ser
 1 5 10 15

Leu Asp

<210> 131

<211> 72

<212> PRT

<213> Artificial Sequence

<220>

<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 131

Cys Gln Cys Arg Arg Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala
 1 5 10 15

Arg Asp Thr Tyr His Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His
 20 25 30

Gly Arg Tyr Val Pro Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys
 35 40 45

Val Ser Ala Gly Asn Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala
 50 55 60

Val Ala Ala Thr Ser Ala Asn Leu
 65 70

<210> 132

<211> 68

<212> PRT

<213> Artificial Sequence

<220>

<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 132

Cys Gln Cys Arg Arg Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala
 1 5 10 15

Arg Asp Thr Tyr His Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His
 20 25 30

Gly Arg Tyr Val Pro Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys
 35 40 45

Val Ser Ala Gly Asn Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala
 50 55 60

Val Ala Ala Thr
 65

<210> 133
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE
 <400> 133

Ala Ala Ala Ser Ala Asn Leu
 1 5

<210> 134
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE
 <400> 134

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ala Val Ala Ala Thr
 1 5 10 15

Ser Ala Asn Leu
 20

<210> 135
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE
 <400> 135

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ala Val Ala Ala Ala
 1 5 10 15

Ser Ala Asn Leu
 20

<210> 136
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
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 <400> 136

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ala Arg Gly Asp Arg
 1 5 10 15

Lys Arg Ile Val
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<210> 137
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE
 <400> 137

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Gln Asp Glu Glu Glu
 1 5 10 15

Gly Ile Trp Ala
 20

<210> 138
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
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 <400> 138

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ala Val Ala Ala Thr
 1 5 10 15

Ser Ile Asn Leu
 20

<210> 139
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>

<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 139

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ala Val Ala Ala Thr
1 5 10 15

Tyr Ser Asn Leu
20

<210> 140

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 140

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ala Arg Gly Asp Arg
1 5 10 15

Lys Arg Trp Ala
20

<210> 141

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 141

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ala Arg Gly Asp Arg
1 5 10 15

Lys Arg Trp Leu
20

<210> 142

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 142

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ala Arg Ser Asp Arg
1 5 10 15

Gly Ile Trp Ala
20

<210> 143
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 143

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ala Val Ala Ala Thr
1 5 10 15

Gly Ile Trp Ala
20

<210> 144
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 144

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Gln Asp Glu Glu Glu
1 5 10 15

Thr Ile Trp Ala
20

<210> 145
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 145

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ala Arg Ser Asp Arg
1 5 10 15

Thr Ile Trp Ala
20

<210> 146
<211> 20

<212> PRT
 <213> Artificial Sequence

<220>
 <223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 146

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ala Arg Ser Asp Arg
 1 5 10 15

Thr Ile Ile Ala
 20

<210> 147
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 147

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ala Arg Ser Asp Arg
 1 5 10 15

Lys Arg Ile Ala
 20

<210> 148
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 148

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ser Arg Thr Asp Arg
 1 5 10 15

Lys Tyr Trp Ala
 20

<210> 149
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 149

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Gln Asp Glu Glu Glu
 1 5 10 15

Gly Ile Trp Ser
 20

<210> 150
 <211> 20
 <212> PPT
 <213> Artificial Sequence

<220>
 <223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE
 <400> 150

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ser Arg Thr Val Arg
 1 5 10 15

Glu Ile Trp Ala
 20

<210> 151
 <211> 20
 <212> PPT
 <213> Artificial Sequence

<220>
 <223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE
 <400> 151

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ser Val Thr Ser Thr
 1 5 10 15

Ser Ile Asn Leu
 20

<210> 152
 <211> 20
 <212> PPT
 <213> Artificial Sequence

<220>
 <223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE
 <400> 152

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ala Arg Gly Asp Arg
 1 5 10 15

Lys Ile Arg Val
 20

<210> 153
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 153

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ala Arg Thr Asp Arg
1 5 10 15

Lys Val Glu Val
20

<210> 154
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 154

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ala Arg Gly Asp Arg
1 5 10 15

Lys Tyr Ile Val
20

<210> 155
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 155

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ser Arg Thr Asp Arg
1 5 10 15

Lys Tyr Gln Ile
20

<210> 156
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 156

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ala Arg Gly Asp Val
1 5 10 15

Arg Leu Met Leu
20

<210> 157
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 157

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ala Arg Gly Asp Arg
1 5 10 15

Lys Val Pro Val
20

<210> 158
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 158

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Gln Asp Glu Arg Arg
1 5 10 15

Leu Ile Val Leu
20

<210> 159
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 159

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ala Arg Gly Asp Arg
1 5 10 15

Leu Val Ser Leu
20

<210> 160
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 160

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ala Arg Gly Thr Arg
1 5 10 15

Leu Val Trp Val
20

<210> 161
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 161

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ala Arg Gly Asp Arg
1 5 10 15

Tyr Arg Ile Val
20

<210> 162
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 162

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ser Arg Thr Asp Arg
1 5 10 15

Leu Glu Tyr Val
20

<210> 163

<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 163

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ala Arg Gly Asp Arg
1 5 10 15

Leu Glu Ile Val
20

<210> 164
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 164

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ala Arg Gly Asp Arg
1 5 10 15

Thr Ile Ile Tyr
20

<210> 165
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 165

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ala Arg Gly Asp Arg
1 5 10 15

Arg Arg Ile Val
20

<210> 166
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 166

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ala Arg Gly Asp Arg
1 5 10 15

Lys Lys Ile Val
20

<210> 167

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 167

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ala Arg Ser Asp Arg
1 5 10 15

Lys Arg Ile Val
20

<210> 168

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 168

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Lys Asn Lys Asp Lys
1 5 10 15

Glu Tyr Tyr Val
20

<210> 169

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 169

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Gly Met Thr Ser Ser
1 5 10 15

Ser Ser Val Val

20

<210> 170
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 170

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Ala Arg Gly Arg Arg
1 5 10 15

Glu Thr Trp Val
20

<210> 171
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 171

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Gln Asp Glu Arg Val
1 5 10 15

Glu Thr Arg Val
20

<210> 172
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 172

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Leu Gln Arg Arg Arg
1 5 10 15

Glu Thr Gln Val
20

<210> 173
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
 <223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 173

Ser Pro Gln Pro Asp Ser Thr Asp Asn Asp Asp Tyr Asp Asp Ile Ser
 1 5 10 15

Ala Ala

<210> 174
 <211> 19
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 174

Pro Tyr Gly Thr Ala Met Glu Lys Ala Gln Leu Lys Pro Pro Ala Thr
 1 5 10 15

Ser Asp Ala

<210> 175
 <211> 19
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 175

His Lys Ala Glu Ile His Ala Gln Pro Ser Asp Lys Glu Arg Leu Thr
 1 5 10 15

Ser Asp Ala

<210> 176
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 176

Pro Lys Gln Ala Asn Gly Gly Ala Tyr Gln Lys Pro Thr Lys Gln Glu

1. 5. 10 15

Glu Phe Tyr Ala
20

<210> 177
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 177

Ala Ile Ser Gly Thr Ser Ser Asp Arg Gly Tyr Gly Ser Pro Arg Tyr
1 5 10 15

Ala Glu Val

<210> 178
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 178

Ileu Asn Ser Cys Ser Asn Arg Arg Val Tyr Lys Lys Met Pro Ser Ile
1 5 10 15

Glu Ser Asp Val
20

<210> 179
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 179

Ala Arg Lys Ala Asn Met Lys Gly Ser Tyr Ser Leu Val Glu Ala Gln
1 5 10 15

Lys Ser Lys Val
20

<210> 180
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 180

Ile Ser Gly Thr Pro Thr Ser Thr Met Val His Gly Met Thr Ser Ser
1 5 10 15

Ser Ser Val Val
20

<210> 181
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 181

Lys Asp Ile Thr Ser Asp Ser Glu Asn Ser Asn Phe Arg Asn Glu Ile
1 5 10 15

Gln Ser Leu Val
20

<210> 182
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 182

Thr Thr Asn Asn Asn Pro Asn Ser Ala Val Asn Ile Lys Lys Ile Phe
1 5 10 15

Thr Asp Val

<210> 183
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 183

Thr Arg Glu Asp Ile Tyr Val Asn Tyr Pro Thr Phe Ser Arg Arg Pro
 1 5 10 15

Lys Thr Arg Val
 20

<210> 184

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 184

Ser Ser Ala Lys Ser Ser Asn Lys Asn Lys Lys Asn Lys Asp Lys Glu
 1 5 10 15

Tyr Tyr Val

<210> 185

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 185

Thr Ser Gly Thr Gly His Asn Gln Thr Arg Ala Leu Arg Ala Ser Glu
 1 5 10 15

Ser Gly Ile

<210> 186

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 186

Gln Gly Asp Pro Ala Leu Gln Asp Ala Gly Asp Ser Ser Arg Lys Glu
 1 5 10 15

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Tyr Phe Ile

<210> 187
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 187

Ser Val Phe Ser Ile Pro Thr Leu Trp Ser Pro Trp Pro Ser Ser
1 5 10 15

Ser Ser Gln Leu
20

<210> 188
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 188

Lys Asp Ser Arg Pro Ser Phe Val Gly Ser Ser Ser Gly His Thr Ser
1 5 10 15

Thr Thr Leu

<210> 189
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 189

His Asp Phe Arg Arg Ala Phe Lys Lys Ile Leu Ala Arg Gly Asp Arg
1 5 10 15

Lys Arg Ile Val
20

<210> 190
<211> 20
<212> PRT

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<213> Artificial Sequence

<220>

<223> DESCRIPTION OF ARTIFICIAL SEQUENCE: SYNTHETIC PEPTIDE

<400> 190

Sex	Thr	Asp	Asn	Leu	Trp	Arg	Pro	Phe	Met	Asp	Thr	Leu	Ala	Sex	His
1			5						10					15	

Gln	Leu	Tyr	Ile
			20